

HYPOIODATE-INDUCED OXIDATIVE DIMERIZATION AND FUNCTIONALIZATION OF THE TROPANE BICYCLIC SYSTEM

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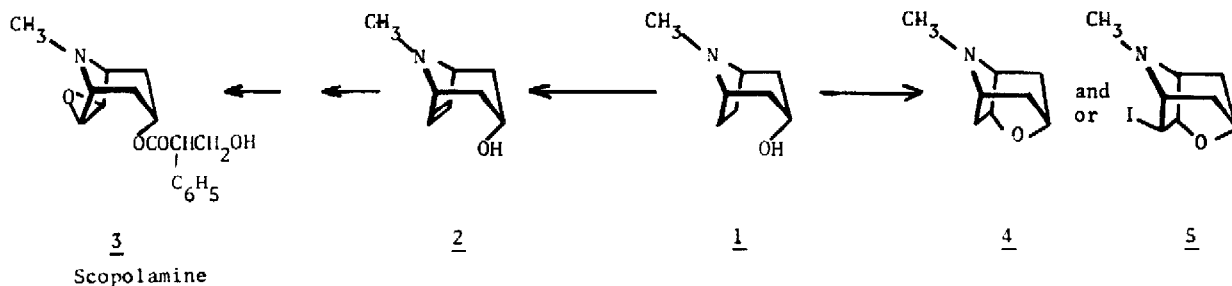
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This study was aimed at exploring whether tropine (1) could be dehydrogenated into 6,7-dehydro-tropan- $\alpha$ -ol (2) a desired key intermediate in scopolamine synthesis ( $1 \rightarrow 2 \rightarrow 3$ ).<sup>1</sup>

In view of the success<sup>2</sup> in functionalizing the  $\delta$  and  $\gamma$  positions of the cholanol sidechain by means of lead tetraacetate (LTA) and iodine ("hypiodate reaction")<sup>3</sup>, we deemed it of interest to apply this method to tropine to induce the reaction sequence  $1 \rightarrow 4 \rightarrow 5$ .

When (1) (0.1 mole) was exposed to the action of LTA (0.2 moles) and iodine (0.1 mole) in  $C_6H_6$  (100 ml) at r.t. for a few hrs., a complex mixture was obtained. Two main groups of products, essentially in equimolar quantities were separated from this mixture by fractional crystallization coupled with column chromatography. One group consisted of a mixture of two iodo-acetoxy-tropines, (15) and (16), accompanied by small amounts of tropinone, and the second one comprised a mixture of four dimers, 8, 9, 10 and 11, each containing two nortropine units combined *via* a carbonyl group.



The most abundant dimeric product, mp 144-146°, (19%) was shown to have the N-(tropan-3 $\alpha$ -yloxy-carbonyl)-nortropan- $\alpha$ -ol structure (8) on the basis of its spectroscopic properties [ $m/e$  294 ( $C_{16}H_{26}O_3N_2, M^+$ ), base peak at  $m/e$  124 ( $C_8H_{14}N$ );  $\nu_{CO}$  1690  $cm^{-1}$ ; nmr ( $CDCl_3$ ):  $\tau$  7.73 (N- $CH_3$ ), 6.9 ( $H^1+5^1$ ), 5.8 ( $H^5$ ), 5.55 ( $H^1+H^6$ ), 5.4 ( $H^3$ ) and 5.05 ( $H^{3'}$ )] and its lithium aluminium hydride (LAH) reduction to give tropan- $\alpha$ -ol as the sole reaction product.

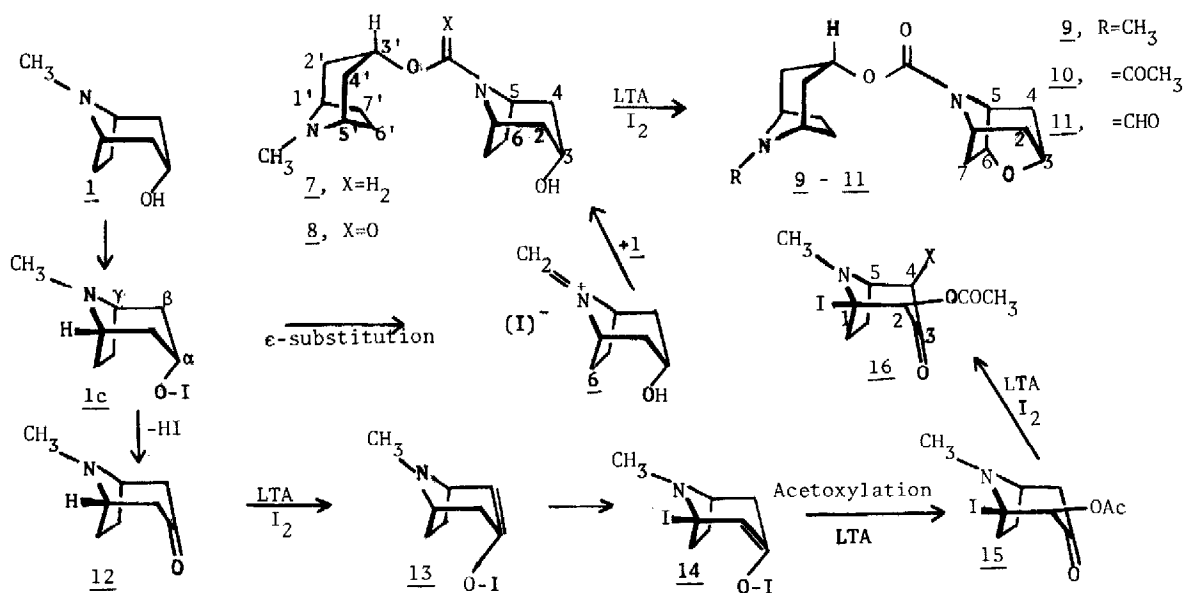
The next major product (11%) analyzed as a  $C_{16}H_{24}O_3N_2$  compound and is assigned the N-(tropan-3' $\alpha$ -yloxy-carbonyl)-nortropan-3,6-oxide structure (9) on the basis of its chemical and spectroscopic properties.

On LAH reduction (9) furnished a 1:1-mixture of (1) and the known tropan-3,6-oxide (4),<sup>4</sup> indicating the presence of an oxygen bridge between the 3 and 6 positions. This structure is consistent with its ir (KBr) absorptions at 1690 (C=O), 1060, 1045 and 1035  $cm^{-1}$  (C-O), and nmr ( $CDCl_3$ ) resonances at  $\tau$  7.72 (N- $CH_3$ ), 6.9 ( $H^{1'}+H^{5'}$ ), 5.9 ( $H^3$ ), 5.75 ( $H^1+H^5$ ) and 5.05 ( $H^{3'}$ ).

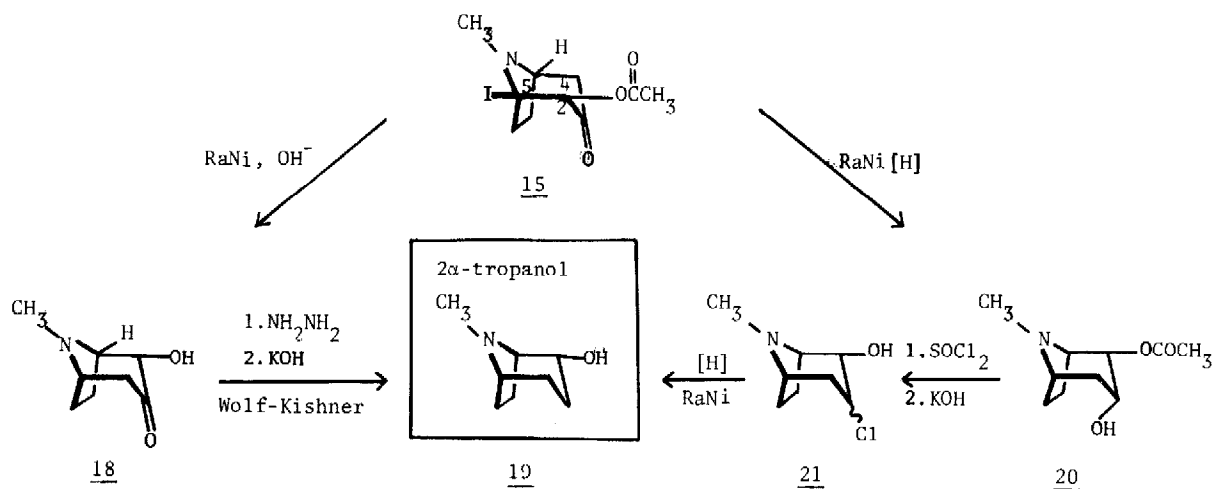
The molecular ion peak at  $m/e$  124 is about the same, apparently because the mass spectral fragmentation occurs at the  $C^{3'}$ -CO bond with retention of the charge on the tropylium ion.

The third dimeric product (7.5%) analyzed as a  $C_{17}H_{24}O_4N_2$  compound and yielded on LAH reduction a 1:1-mixture of (17) and N-ethyl-nortropine,<sup>5</sup> indicating that it must be of the

SCHEME 1



SCHEME 2



N'-(acetylnortropan-3 $\alpha$ -yloxycarbonyl)-nortropan-3,6-oxide structure (10). Its ir (neat) absorptions at 1690 (N-CO-O), 1620 (N-COCH<sub>3</sub>), 1040 and 1080 cm<sup>-1</sup>, and nmr (CDCl<sub>3</sub>) resonances at  $\tau$  7.95 (CH<sub>3</sub>-N), 5.85 (H<sup>5</sup>+H<sup>5'</sup>+H<sup>6</sup>), 5.45 (H'+H<sup>3</sup>), 5.36 (H<sup>1'</sup>) and 4.93 (H<sup>3'</sup>) are consistent with the structure assigned. The mass spectrum of (10) exhibits the molecular-ion peak at m/e 320 (3%) and peaks at 168 (29%), 152 (44%), 110 (52%) and 83 (100% base peak).

The minor product (2.5%) is assigned the (N'-formyl-nortropanyloxycarbonyl)-nortropan-3,6-oxide formulation (11) on the basis of its: (i) elementary analysis; (ii) its ir spectrum (KBr): 1688 (N-CO-O), 1662 (N-CHO), 1035 and 1070 cm<sup>-1</sup>; (iii) its nmr spectrum (CDCl<sub>3</sub>):  $\tau$  5.9 (H<sup>5</sup>+H<sup>5'</sup>), 5.45 (H<sup>1</sup>+H<sup>1'</sup>, 3, 6) 4.90 (H<sup>3'</sup>) and 1.87 (CHO); (iv) its LAH reduction, giving (1) as the sole reaction product. It exhibits molecular-ion peak at m/e 306 (5%) and peaks at 154 (50%), 138 (81%), 110 (100%, base peak).

Treatment of (8) similarly with LTA and iodine afforded (9) in high yield. This strongly suggests that the latter and probably (10) also originate in the process from (8).

Another major product (16) (m.p. 185°) analyzed as C<sub>10</sub>H<sub>13</sub>I<sub>2</sub>NO<sub>3</sub> compound, exhibiting ir (KBr) absorptions at 1730 (ester), 1745 and 1760 cm<sup>-1</sup> (C=O) and nmr resonances (CDCl<sub>3</sub>) at  $\tau$  7.95 (3H, s, COCH<sub>3</sub>), 7.25 (3H, s, N-CH<sub>3</sub>), 6.32 (1H, q, H<sup>5</sup>), 5.45 (1H, s, H<sup>4</sup>), 4.75 (1H, dd, H<sup>2</sup>, J<sub>2,7</sub> *endo* 11 Hz, J<sub>2,7</sub> *exo* 4 Hz).<sup>6</sup> The 4 $\beta$  iodine substituent in (16) is easily de-iodinated on short treatment with aqueous sodium bisulphite, affording the mono-iodo ketoester (15). The data presented are consistent with 1 $\alpha$ ,4 $\beta$ -di-iodo-2 $\alpha$ -acetoxytropan-3-one (16) formulation.

The minor product (m.p. 137°) analyzed as a C<sub>10</sub>H<sub>14</sub>INO<sub>3</sub> compound and is assigned the 1 $\alpha$ -iodo-2 $\alpha$ -acetoxytropan-3-one (15) structure on the basis of following chemical and spectroscopic evidence. Its ir spectrum (KBr) displays bands at 1730 and 1760 cm<sup>-1</sup> (keto-ester) and its nmr (CDCl<sub>3</sub>) spectrum exhibits signals at  $\tau$  7.92 (3H, s, COCH<sub>3</sub>), 7.25 (3H, s, N-CH<sub>3</sub>), 6.25 (1H, m, H<sup>3</sup>) and 4.70 (1H, dd, H<sup>2</sup>, J<sub>2,7</sub> *endo* 11 Hz, J<sub>2,7</sub> *exo* 4 Hz).<sup>7</sup>

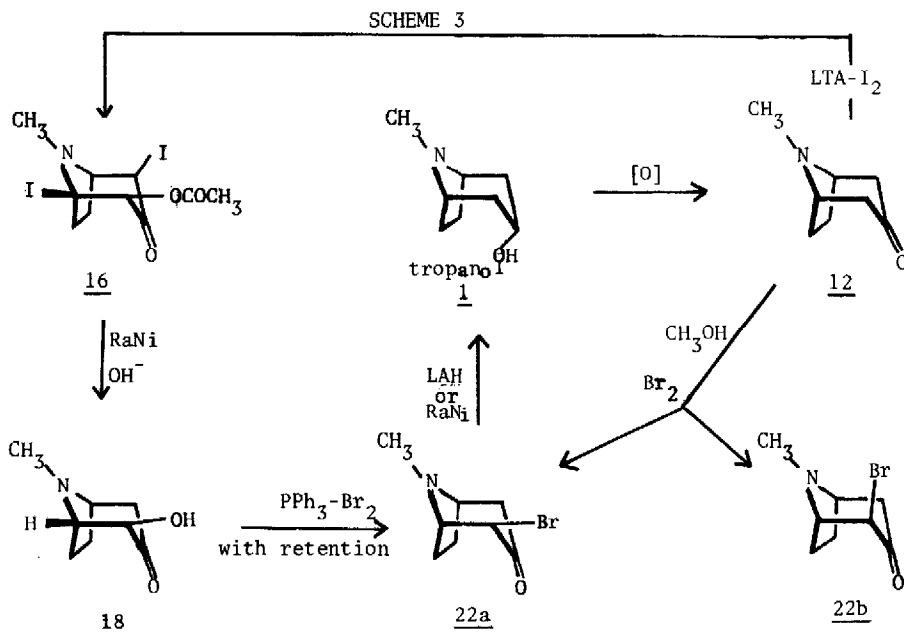
The sites of attachment and the stereochemistry of the iodo and acetoxy substituents in (16) were deduced from its transformation into 2 $\alpha$ -tropanol following two independent routes as delineated in Scheme 2. The bridgehead iodine is first hydrogenolyzed by means of Raney Nickel in alkaline solution to give the ketol (18) (m.p. 101-103°) which on Wolff-Kishner reduction afforded 2 $\alpha$ -tropanol (19) (m.p. 46-48°)<sup>8</sup>; the hydrochloride salt melted at 266°. Alternatively, catalytic reduction of (16) to form (20) (m.p. 79-80°) followed by chlorination and catalytic reduction provided (19).

The mass spectrum of (16) is characterized by the three primary mass spectrum reactions: A - loss of ethylene to yield the respective acetoxy-iodo-N-methyl-pyridone (base peak); B - Loss of ketene to yield the corresponding iodo-tropanone; C - loss of iodine which is followed by successive losses of ethylene and ketene to yield pyrrolidone derivatives.<sup>9</sup>

The formation of (8) - (11) and of (15) - (16) could be envisioned as arising from 3 $\alpha$ -tropanol hypoiodate (1a) which gives rise equally to two distinctly different modes of inner radical displacement reactions at  $\alpha$  and  $\epsilon$  positions, to yield tropanone (actually isolated in 0.5% yield) and N-(iodomethyl)-tropine (6), respectively (Scheme 1). The conversion of (9) into (16) and (15) could be viewed as pursuing the route 12 + 13 + 14 + 15 + 16. Intermediate (6)

would react in an ylide form with another molecule of (1) to form (7) which is further oxidized to produce (8) - (11).

The location of the carbonyl at 3 position is inferred from the reaction sequence  $15 + 18 \rightarrow 22 \rightarrow 1$  (the hydrobromide salt of 22 melted at 288-290°) (Scheme 3). It could be shown that tropanone is the likely precursor of (16).



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