

STUDIES ON ( $\pm$ ) PSEUDOPELLETIERINE OXIME\*

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## ABSTRACT

Pseudopelletierine oxime has been found to possess molecular asymmetry and this has been confirmed by the resolution of (+)-pseudopelletierine oxime. Beckmann rearrangement of the ( $\pm$ )-oxime yielded 10-methyl-3,10-diazabicyclo [4.3.1] decan-4-one.

THE enantiomerism of 4-methylcyclohexylideneacetic acid<sup>1</sup> and other doubly bonded cyclohexylidene derivatives such as oximes, semicarbazones, and phenylhydrazones is well known<sup>2,3</sup>. Geometrical enantiomerism is also operative in an oxime of a ketone of the type  $A^R\text{-CO-}A^S$ , where  $A$  is a dissymmetric group. The first illustration of this was provided by Lyle and Lyle<sup>4</sup> who showed the oxime of *cis*-2,6-diphenyl 1-methyl-4-piperidone to be racemic, for it could be resolved. Lyle and Pelosi<sup>5</sup> have also proven the absolute configuration of the resolved oxime (I). The resolution of (–)-tropinone oxime (II) by Singh and Razdan<sup>6</sup> is another recorded illustration of such an enantiomerism.

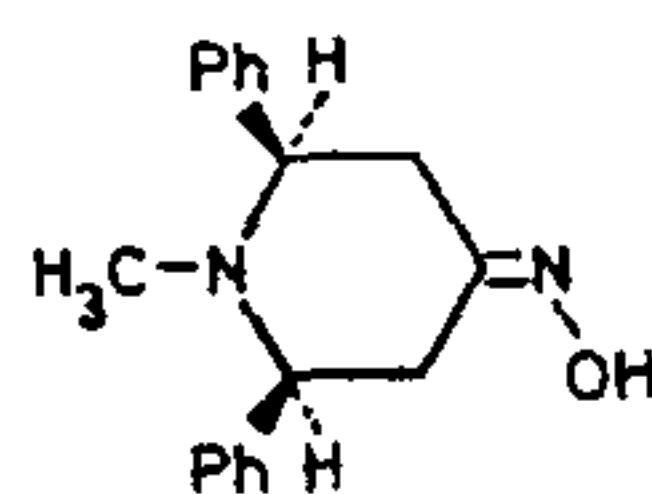
Pseudopelletierine (III) like tropinone is an internally compensated molecule. It was envisaged that its oxime like that of tropinone oxime will also be racemic. In the present communication its oxime (IV) has been shown to be racemic by resolving the (+)-pseudopelletierine oxime. The resolution was effected by fractional crystallization of the camphor-10-sulfonate salt. Attempts to obtain the levorotatory isomer, however, were not successful. Further the racemic oxime was subjected to Beckmann rearrangement. Out of the various methods employed, the reaction was successful with *p*-acetamidobenzene-sulfonyl chloride/pyridine system<sup>7</sup> yielding 10-methyl-3, 10-diazabicyclo[4.3.1] decan-4-one (V). Paquette and Wise<sup>8</sup> obtained the lactam (V) by Schmidt reaction with pseudopelletierine (III). The lactam thus obtained was next reduced with lithium aluminium hydride in tetrahydrofuran to yield 10-methyl-3, 10-diazabicyclo[4.3.1]decane (VI). Sasaki *et al*<sup>9</sup> obtained (VI) by isolating the tris-aluminium complex and then decomposing it with hydrochloric acid. Our repeated attempts to isolate the tris-aluminium com-

plex, however, were unsuccessful. Work on the configuration of the resolved oxime is in progress.

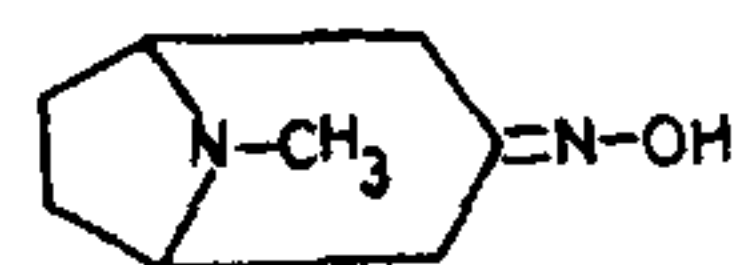
## Experimental

All the melting points are uncorrected.

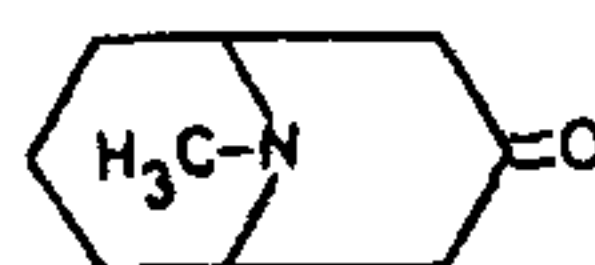
*Pseudopelletierine*<sup>7</sup> (III): To a solution of acetonedicarboxylic acid<sup>10</sup> (85.0 g) in water were added glutaraldehyde (230.0 ml; 25% W/W solution), methylamine hydrochloride (39.1 g), and sodium acetate (175.5 g) and final volume was made to 6.25 l with water. The pH of the solution was next adjusted to 4, and the solution allowed to stand at room temperature



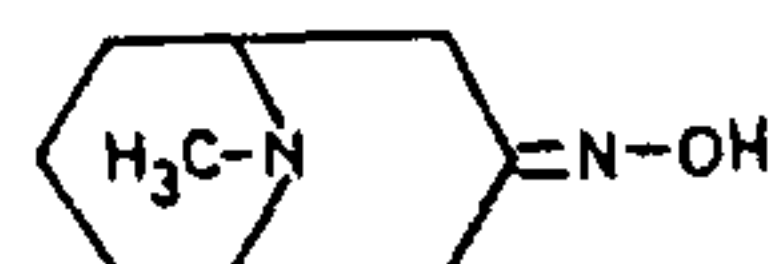
(I)



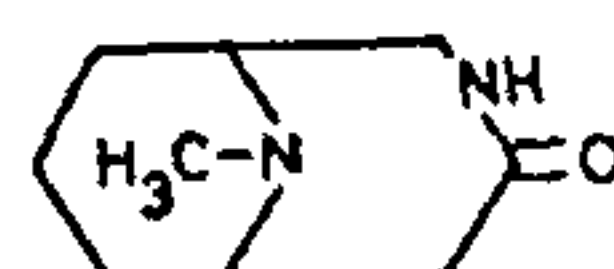
(II)



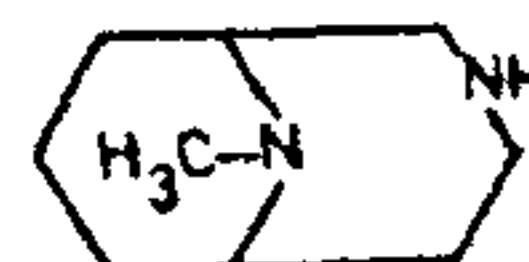
(III)



(IV)



(V)



(VI)

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for 3 days. The resulting solution which was acidic to litmus was basified with potassium carbonate, saturated with sodium chloride, and extracted with chloroform (4 × 400 ml). The chloroform extract after working up yielded a reddish oil (26 g). The latter on crystallization from petroleum ether (60–80°) afforded needles; yield 21.5 g (23.6%); mp 46° (lit<sup>11</sup> 45°).

(±)-*Pseudopelletierine oxime*<sup>7</sup> (IV): To a mixture of pseudopelletierine (III) (4.0 g) in aqueous solution of potassium hydroxide (8.75 g in 16 ml) was added an aqueous solution of hydroxylamine hydrochloride (3.63 g in 8 ml). The reaction mixture was shaken and allowed to stand at room temperature. After 48 hr it was saturated with carbon dioxide when an oily mass was separated. The mixture was next saturated with potassium carbonate and the separated oil extracted with ether (4 × 150 ml). The ether solution after processing afforded a solid residue. Crystallization of the residue gave needles of (±)-pseudopelletierine oxime, which did not show optical activity; yield 3.4 g (77.4%); mp 128° (lit<sup>11</sup> 126–7°) (Found: C, 64.22; H, 9.78; N, 16.15. C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>O requires C, 64.25; H, 9.58; N, 16.65%).

(+)-*Pseudopelletierine oxime*: To a suspension of (+)-10-camphorsulfonic acid (5.5 g) in dry ether (55.0 ml) was added methanol till a clear solution was obtained. Addition of an ether-solution of (±)-pseudopelletierine oxime (IV) (4.0 g in 100 ml) afforded camphorsulfonate salt which separated as needles; yield 7.0 g (73.7%); mp 235° (dec.). Fractional crystallization of the salt from methanol-ether yielded 2.3 g of diastereoisomer mp 235° (dec.);  $[\alpha]_D^{31} + 30^\circ$  (c. 1.7 in methanol), (Found: C, 57.23; H, 8.23; N, 7.49. C<sub>19</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>S requires C, 56.97; H, 8.05; N, 6.99%).

The resolved oxime was isolated from the diastereomer (1.0 g) by basifying its aqueous solution with potassium carbonate, saturating with sodium chloride, and extracting with ether (4 × 10 ml). The ether extract after working up and crystallization from petroleum ether (60–80°) gave needles; yield 0.35 g; mp 128°;  $(\alpha)_D^{31} + 16^\circ$  (c, 1.4 in methanol), Found: C, 64.40; H, 9.75; N, 16.27. C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>O requires C, 64.25; H, 9.58; N, 16.65%.

10-Methyl-3, 10-diazabicyclo [4.3.1]decan-4-one (V): Solid *p*-acetamidobenzenesulfonyl chloride (3.0 g) was added to a solution of (±)-pseudopelletierine oxime (IV) (1.0 g) in anhydrous pyridine (13.0 ml). The reaction mixture which became clear after shaking was left at room temperature for 4 hr. It was next poured with stirring into crushed ice (50 g). Removal

of water and pyridine under vacuum on a water bath yielded a sticky mass. The residue was next taken up in water (15.0 ml), basified with potassium carbonate and then with aqueous potassium hydroxide (6.0 ml of 60% W/V). The alkaline solution was next extracted with chloroform (4 × 30 ml) which on further processing gave crude lactam (0.7 g). Crystallization from petroleum ether (60–80°) afforded needles; yield 0.4 g (40%); mp 162–4° (lit<sup>7</sup> 164–6°), (Found: C, 64.17; H, 9.79; N, 16.82. C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>O requires C, 64.25; H, 9.58; N, 16.65%). IR (Nujol) 3170 (lactam N–H stretching), 1650 cm<sup>-1</sup> (C=O stretching).

This product was comparable with the one obtained by Schmidt reaction<sup>8</sup> of pseudopelletierine.

10-Methyl-3, 10-diazabicyclo [4.3.1]decan-4-one (VI): To a refluxing suspension of lithium aluminium hydride (5.1 g) in dry tetrahydrofuran (50.0 ml) was added a solution of 10-methyl-3, 10-diazabicyclo [4.3.1]decan-4-one (V) (8.2 g) in dry tetrahydrofuran (150.0 ml). After refluxing for 48 hr, the excess of lithium aluminium hydride was destroyed by adding a mixture of tetrahydrofuran—water (50%). The mixture was further refluxed for 1 hr and filtered. The filtrate was dried and evaporated to yield a syrupy oil (6.2 g). Distillation of the oil under vacuum yielded 3.08 g (50.6%) of a hygroscopic, sublimable, wax like product; mp 42° (lit<sup>8</sup> 43–6°) (Found: N, 18.45. C<sub>9</sub>H<sub>18</sub>N<sub>2</sub> requires N, 18.17%). Attempts to isolate the tris-aluminium complex, as reported in literature<sup>8</sup>, were unsuccessful.

The dihydrochloride of the amine (VI) was prepared in the usual manner and crystallized from absolute ethanol; mp 180–2° (dec.); (Found: C, 47.34; H, 8.92; N, 12.61. C<sub>9</sub>H<sub>20</sub>N<sub>2</sub>Cl<sub>2</sub> requires C, 47.58; H, 8.87; N, 12.33%). IR (KBr) 2925 (C–H and N–H stretching in NH<sub>2</sub><sup>+</sup>), 2505 (N–H stretching in NH<sup>+</sup> group), and 1555 cm<sup>-1</sup> (N–H bending).

#### ACKNOWLEDGEMENT

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## NEWS

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### LEPROSY: BEGINNING OF THE END

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