

THE OPTICAL ROTATION OF MITRAPHYLLINE

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(Received 13 January 1966)

Mitraphylline has been reported to occur in the d-, l- and dl- forms [Michiels¹ $[\alpha]_D^{20} \pm 0$ (C. 0.64, CHCl_3), Raymond Hamet² $[\alpha]_D^{20} - 7.7$ to -9.8° (no details), Badger, Cook and Ongley³ and Ongley⁴ $[\alpha]_D \pm 0$ (no details), $[\alpha]_D^{21} + 7.1^\circ$ (C. 1.96, CHCl_3), $[\alpha]_D^{21} + 4.6^\circ$ (C. 0.98, CHCl_3) $[\alpha]_D^{21} - 7.4^\circ$ (C. 1.22 CHCl_3), Nozoye⁵ $[\alpha]_D + 3.8^\circ$ and Seaton, Tondeur and Marion⁶ $[\alpha]_D - 3.0$ (C. 1.3 CHCl_3). This led Finch and Taylor⁷ to suggest that as oxindole alkaloids of this type readily equilibrate into a mixture of the parent alkaloid and its epimer, it is possible that the apparent isolation of the d- and dl- mitraphylline is due to contamination of the l-mitraphylline $[\alpha]_D - 7^\circ$ (CHCl_3) with its isobase $[\alpha]_D^{20} + 18^\circ$ (CHCl_3).

Equilibration of mitraphylline \rightleftharpoons isomitraphylline, in vitro, requires refluxing in pyridine or 50% acetic acid for 36 - 48 hours and as extraction procedures are rarely as drastic as this it is unlikely that sufficient epimer is produced by isomerisation during the isolation of the alkaloid to affect, very seriously, the $[\alpha]_D$ of the isolated alkaloid. In our equilibration experiment no epimerisation of either mitraphylline or isomitraphylline occurred, at room temperature, in 96% ethanol, chloroform, 5% acetic acid or with 20% ammonium hydroxide, these being the reagents used in our extraction procedures. It would require a mixture of approximately 55% isomitraphylline with the mitraphylline to give $[\alpha]_D + 7^\circ$, approximately 43% to give $[\alpha]_D + 3.8^\circ$, approximately

28% to give $[\alpha]_D^0$ and approximately 10% to give $[\alpha]_D^+ - 3.0^\circ$. However, mitraphylline crystallises readily from absolute ethanol but isomitraphylline which occurs only in the amorphous state is readily soluble in ethanol and indeed most common organic solvents, so that it is unlikely to be present with mitraphylline obtained by crystallisation. In our isomerisation experiments, two recrystallisations only, from absolute ethanol were sufficient to give us mitraphylline $[\alpha]_D^{20} - 7.1$ (C, 2, CHCl₃) completely free from isomitraphylline as shown by several T.L.C. systems.

It is interesting that no one, until recently, has reported the presence of naturally occurring isomitraphylline. Now, not only mitraphylline $[\alpha]_D^{23} - 7.1$ (C, 2, CHCl₃) but isomitraphylline $[\alpha]_D^{21} + 18.4$ (C, 2, CHCl₃) and a hitherto undescribed isomer of mitraphylline which has been named speciophylline $[\alpha]_D^{21} + 91.3$ (C, 0.21, CHCl₃) has been isolated from the leaves of Mitragyna speciosa Korth⁸. As speciophylline crystallises readily from absolute ethanol it is possible that it was this alkaloid which was responsible for the false optical rotations of mitraphylline. A mixture of approximately 15% speciophylline with mitraphylline would be required to give an $[\alpha]_0 + 7^\circ$, approximately 11% to give $[\alpha]_D + 3.8^\circ$, approximately 7.5% to give $[\alpha]_0^+ 0$ and approximately 5% to give $[\alpha]_D - 3.0$.

While it is easy to distinguish between mitraphylline and isomitraphylline by thin layer chromatography, it is not always easy to distinguish between mitraphylline and speciophylline and it is necessary to employ several systems including Alumina/CHCl₃ and Silica gel/CHCl₃:(CH₃)₂CO, 5:4. A mixture of mitraphylline and speciophylline when examined by thin layer chromatography with Silica gel/EtOH:CHCl₃, 9:1 as used by Finch and Taylor⁷ does not always show complete separation.

The alternate explanation offered by Finch and Taylor⁷ that some of the differences in the reported $[\alpha]_D$ may be due to errors attendant in measuring small isolations in inadequate concentration is a valid one and it would be preferable if details of the O.R.D. curve were given.

Our materials gave the following data -

Mitraphylline [dioxan, C, 0.132]

$[\alpha]_{589} - 8.3^\circ$, $[\alpha]_{450} \pm 0^\circ$, $[\alpha]_{400} + 20^\circ$
 $[\alpha]_{340} + 200^\circ$, $[\alpha]_{315} + 676^\circ$ $[\alpha]_{312} + 758^\circ$

Isomitraphylline [dioxan, C, 0.130]

$[\alpha]_{589} + 27^\circ$, $[\alpha]_{450} + 18^\circ$, $[\alpha]_{400} - 35^\circ$
 $[\alpha]_{340} - 240^\circ$, $[\alpha]_{315} - 761^\circ$, $[\alpha]_{312} - 1230^\circ$

Speciophylline [dioxan, C, 0.10]

$[\alpha]_{589} + 77^\circ$, $[\alpha]_{450} + 125^\circ$, $[\alpha]_{400} + 155^\circ$
 $[\alpha]_{340} + 209^\circ$ (max.), $[\alpha]_{315} + 71^\circ$, $[\alpha]_{312} \pm 0$

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We thank Mr. G. McDonough for the O.R.D. measurements.