

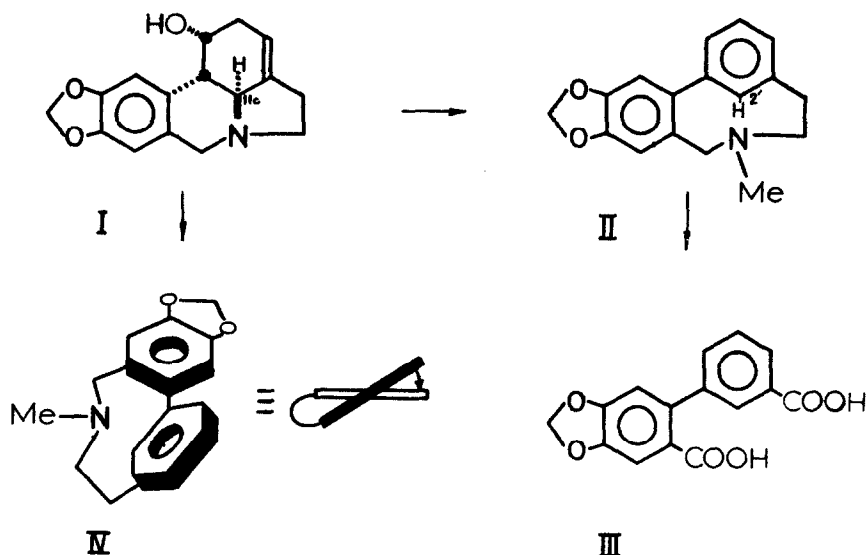
A ONE-STEP CONVERSION OF CARBON ATOM ASYMMETRY
INTO BIPHENYL ASYMMETRY AND ITS RELATION TO THE
ABSOLUTE CONFIGURATION OF CARANINE

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The alkaloid caranine, whose structure and relative stereochemistry (represented in I) are known from degradative work (1,2,3), spectra (4), and X-ray analysis (5), has recently been assigned the absolute stereochemistry depicted in I on the basis of ORD and CD measurements on some lycorine derivatives (4). In this Letter is reported a conversion of caranine into an asymmetric biphenyl whose absolute configuration is shown to be that of IV based on the absolute stereostructure I.

Earlier, Hofmann degradation of caranine methiodide yielded an anhydromethine, m.p. 91-92.5°, proved to have the structure II by further degradation and by permanganate oxidation to III which was identical with a synthetic specimen (1). Examination of a Stuart-Briegleb model of II revealed that the four atom o,m'-bridge would have difficulty in moving past the 2'-hydrogen and, therefore, suggested that the anhydromethine might be capable of existence in enantiomeric forms. In this event, since elimination of nitrogen during the Hofmann reaction would necessarily occur from one side of ring C in the



methiodide of I, only one of the two possible atropisomers would be formed.

However, the anhydromethine II from the Hofmann reaction at 120° was optically inactive (1). To test whether structure II could support optical activity, the anhydromethine was treated at room temperature with di-*p*-toluyl-L-tartaric acid. From the salt obtained, m.p. $150-154^\circ$, was regenerated the anhydromethine which now melted at $73-76^\circ$ and rotated polarized light, $[\alpha]_D + 21^\circ$ (c , 0.95 in CHCl_3).

The explanation for the lack of optical activity in II from the Hofmann elimination at 120° was found in the facile racemization of resolved II. When optically active II was slowly heated above its melting point, it resolidified and melted at $92-92.5^\circ$ yielding racemic II; it was also racemized upon heating for a few minutes in boiling methanol. Nevertheless, the optical stability of II at room temperature prompted the use of milder conditions for the Hofmann reaction with the hope of isolating optically active II.

A mixture of caranine α - and β -methiodides (550 mg.) was added to a solution of sublimed potassium *t*-butoxide (300 mg.) in 10 ml. of dry dimethylsulphoxide and stirred at room temperature for 36 hr. Dilution with water and extraction with ether and benzene

gave 305 mg. (86%) of a mixture of products. Separation by thick layer chromatography on silica gel developed in ethanol:chloroform (2:98) yielded 25 mg. of optically active caranine anhydromethine [m.p. 82-83°, $[\alpha]_D^{20}$ -27° (c, 1.45 in CHCl₃) after re-chromatography] which was shown (IR, UV, TLC) to be identical in structure with an authentic sample of racemic II. This reaction constitutes the conversion of a compound with four asymmetric atoms into an asymmetric biphenyl with no asymmetric atoms remaining (7).

If the absolute configuration of II is to be related to that of I, the configuration of the nitrogen atom at the instant of elimination must be known. When the Hofmann reaction was performed in dimethylsulfoxide-d₆ (DMSO-d₆), up to four atoms of D/molecule (mass spectrum) were incorporated into the anhydromethine whose NMR spectrum showed C-11c to be one of the sites of replacement. To find out whether the hydrogen at C-11c was exchanged before Hofmann elimination (via an ylide)(8), a reaction was run in DMSO-d₆ on caranine β-methiodide,* m.p. 312-313° (dec.), with only 0.5 equivalent of t-butoxide. The excess methiodide recovered had m.p. 312-313° (dec.), $[\alpha]_D$ +61° (DMF:H₂O, 1:1)[reported (1b): $[\alpha]_D$ +62°], and contained an average of 0.58 D/molecule. The NMR spectrum of the chloride of this material in D₂O revealed that most (~0.4 D) of the deuterium had been introduced at C-11c (δ 4.95). Hence, the hydrogen exchange at C-11c occurred before Hofmann elimination, and although the β-methiodide was in this way offered an opportunity to change its configuration at C-11c, it did not do so. A study of molecular models reveals no reason to consider seriously the remote possibility that caranine β-methiodide is isomerized to the other quaternary C-11c epimer (H up, N down), which then undergoes elimination not only much more rapidly than the unepimerized β-methiodide, but also sufficiently rapidly to prevent its survival in the incomplete reaction described above. When it is further noted that the II from the reaction in DMSO-d₆ still contained 25% of non-deuterated molecules necessarily derived from I without epimerization at C-11c, this remote possibility becomes even more improbable. Consequently, the stereochemistry of the biphenyl II is determined by the configuration of the nitrogen atom in caranine β-methiodide,* and may, therefore, be represented by IV.

* In separate experiments with pure caranine α- and β-methiodides it was found that the α-methiodide (N-Me up) gave little II (~20%), whereas II was the major product (~70%) from the α-methiodide (N-Me down). The α:β methiodide proportions in the mixtures used were such that almost all of the II produced would have come from the β-methiodide.

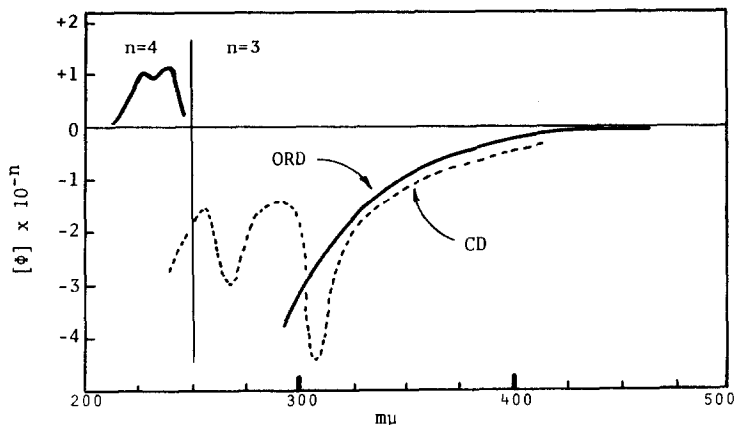


FIG. 1

ORD and CD curves of caranine anhydromethine

The negative sign of the Cotton effect (here centred near 260 $m\mu$) shown by the ORD and CD curves (FIG. 1) of the optically active anhydromethine IV is that predicted by the generalization of Mislow, *et al.*, for the $\pi \rightarrow \pi^*$ transition of simple twisted biphenyls (6). Should future work permit confident extension of the generalization to such biphenyls as IV,[†] the present work would constitute an independent determination of the absolute stereochemistry of caranine and related alkaloids through the use of biphenyl asymmetry.

[†] In a twisted biphenyl such as IV, there is some question whether either of the Cotton effects in FIG. 1 results from the biphenyl $\pi \rightarrow \pi^*$ transition since optically active O-biphenyl $n \rightarrow \pi^*$ and N-biphenyl $n \rightarrow \pi^*$ transitions are also possible. A N-biphenyl $n \rightarrow \pi^*$ origin for either of the Cotton effects is excluded by the lack of change in the CD curve of IV in solution with added perchloric acid. However, we cannot exclude an O-biphenyl $n \rightarrow \pi^*$ origin for one or both of the Cotton effects.

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