The Formation of Optically Active Biphenyls from Schelhammeridine

By S. R. JOHNS, J. A. LAMBERTON, A. A. SIOUMIS, and H. SUARES

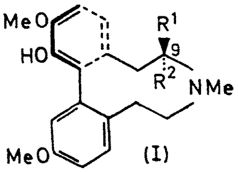
(*Division of Applied Chemistry, C.S.I.R.O., Chemical Research Laboratories, Melbourne, Australia*)

Summary The bridged-(*S*)-biphenyl derivative formed by heating (3*S*,5*S*)-schelhammeridine with acetic anhydride is enantiomeric with one of the diastereoisomeric (*R*)-biphenyls formed by heating schelhammeridine with 10% hydrochloric acid.

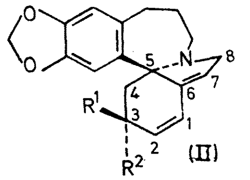
THE reaction between phenylmagnesium bromide and (−)-thebaine gives a mixture of diastereoisomeric phenyldihydrothebaines (Ia, b) that have the same configuration for the dissymmetric biphenyl system and opposite configurations at C-9.[1] On thermal equilibration each diastereoisomer is partly converted into the optical antipode of the *other* diastereoisomer by inversion of the configuration of the biphenyl system. The explanation of the optical properties of the products of this reaction has been widely discussed,[1] and to date no other reaction of this type has been recorded. We report similar, although interestingly different, observations on the derivation of optically active biphenyls from the alkaloid schelhammeridine (IIa).

Schelhammeridine is converted by heating in 10% hydrochloric acid solution at reflux temperature into a mixture of epimeric alcohols (IIb), m.p. 233—235°, $[\alpha]_D + 20°$ in $CHCl_3$; and (IIc), m.p. 167—168°, $[\alpha]_D - 199°$ in $CHCl_3$, and epimeric amino-alcohols (IIIa) and (IIIb). It is suggested that the amino-alcohols are formed by the aromatization of ring A by the mechanism depicted in (IV). The amino-alcohols have been characterized in the form of their respective *N*-acetyl derivatives, which have been shown to be diastereoisomers having the same configuration of the biphenyl system and opposite configurations at C-7.

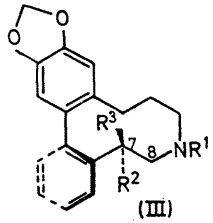
It can be predicted from the known absolute configuration of schelhammeridine[2] that the biphenyl system will have the (*R*)-configuration indicated in (IIIc) and (IIId) provided that the configuration of the initially generated biphenyl system is retained. The assignment of the configuration at C-7 in (IIIc) and (IIId) depends on the assumption of a fully staggered conformation with the least non-bonded interactions for each ten-membered-ring system. Consideration of the dihedral angles and the coupling constants between the C-7 and C-8-protons then allows the following assignments to be made. The *N*-acetyl alcohol, m.p. 264—266°, $[\alpha]_D + 41°$ in $CHCl_3$, $J_{7,8a}$ 4·8, $J_{7,8b}$ 11·0 c./sec. ($\phi_{7,8a} \sim 50°$, $\phi_{7,8b} \sim 180°$), isolated in 3% yield has the configuration (IIIc), and the *N*-acetyl alcohol, m.p. 167—168° and 264—266° (double m.p.), $[\alpha]_D + 100°$ in $CHCl_3$, $J_{7,8a}$ 6·0, $J_{7,8b}$ 5·5 c./sec. ($\phi_{7,8a}$ and $\phi_{7,8b}$ both $\sim 50°$), isolated in 10% yield, has the configuration (IIId). The



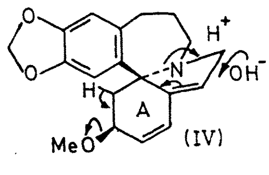
	R1	R2
(a)	H	Ph
(b)	Ph	H

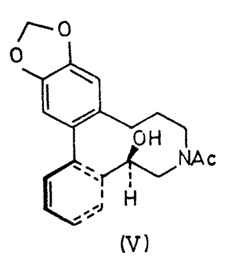


	R1	R2
(a)	OMe	H
(b)	H	OH
(c)	OH	H



	R1	R2	R3
(a)	H	OH	H
(b)	H	H	OH
(c)	Ac	OH	H
(d)	Ac	H	OH





(V)

indications of hydrogen bonding in the i.r. spectrum of (IIId) (double amide carbonyl band at 1615 and 1630 cm.$^{-1}$) support the conformation in which hydrogen bonding between the hydroxy and amide carbonyl groups can occur.

Heating schelhammeridine with acetic anhydride at reflux temperature gives a quantitative yield of an *N,O*-diacetyl compound, which on hydrolysis gives the *N*-acetyl alcohol (V), m.p. 266—267°, $[\alpha]_D - 42°$ in $CHCl_3$, enantiomeric with (IIIc). The i.r. and n.m.r. spectra of (V) and (IIIc) are identical and their o.r.d. spectra are mirror images with opposite signs for the Cotton effects at 250 and 290 nm. The greater stereospecificity in the reaction with acetic anhydride can be explained by a mechanism similar to that shown in (IV) but involving a cyclic intermediate such that the acetyl cation attacking at the nitrogen and the acetoxy-anion attacking at C-7 are derived from the same molecule of acetic anhydride. The configuration of the biphenyl system of the acetic anhydride reaction product (V) is clearly opposite to that of the hydrochloric acid reaction products (IIIc) and (IIId), and experimental evidence is available to show that (V) has been formed by inversion of the biphenyl configuration of the initially generated product, the *O*-acetyl derivative of (IIId). Heating the *N*-acetyl alcohol (IIId) with acetic anhydride at reflux temperature affords the *O*-acetyl derivative of (V), and heating (IIId) in n-pentanol at reflux temperature, or to its first melting point, gives (V) directly. The formation of a single compound (V) contrasts with the thermal equilibration of the phenyldihydrothebaines and presumably depends upon the relief of non-bonded interactions between the 7-hydroxy- and *N*-acetyl groups of (IIId).

The reaction of schelhammeridine with acetic anhydride is unusual in giving a quantitative yield of a product with the configuration of the biphenyl system opposite to that which might be predicted solely on the basis of the known absolute configuration of schelhammeridine. The relationship between the three stereoisomeric *N*-acetyl alcohols (IIIc, IIId, and V) has been confirmed by oxidation with manganese dioxide in each instance to the same optically inactive 7-ketone, m.p. 203—204°. According to the Cahn, Prelog, Ingold system,[3] the configurations of the biphenyl system and of the C-7 centre in (IIIc), (IIId), and (V) can be designated respectively by *R*,7*S*-, *R*,7*R*-, and *S*,7*R*-.

(*Received, April 24th,* 1969; *Com.* 558).

---

[1] L. Small, L. J. Sargent, and A. Bralley, *J. Org. Chem.*, 1947, **12**, 1839; R. Robinson, *Nature*, 1947, **160**, 815; J. A. Berson and M. A. Greenbaum, *J. Amer. Chem. Soc.*, 1958, **80**, 445; H. L. Holmes and G. Stork, in "The Alkaloids," vol. II, ed. R. H. F. Manske and H. L. Holmes, Academic Press, New York, 1952, p. 169; E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 170.

[2] S. R. Johns, C. Kowala, J. A. Lamberton, A. A. Sioumis, and J. A. Wunderlich, *Chem. Comm.*, 1968, 1102. In this communication the structural formula of schelhammeridine was drawn incorrectly without the C-6,C-7 double bond.

[3] R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 1956, **12**, 81.