Conversion of a Protopine into an Indenobenzazepine. Stereoselective Formation of *cis*- and *trans*-B/C Fused Indenobenzazepines

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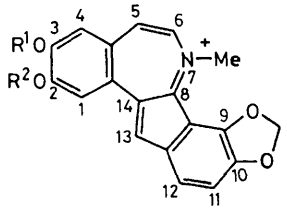
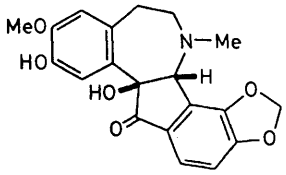
Summary Treatment of the protopine (**7**) with strong base and sunlight yields the *cis*-fused indenobenzazepine (**8**) while reaction of the oxo-aziridine (**9**) with acidic reagents leads to the *trans*-indenobenzazepines (**13**), (**15**), and (**17**), which isomerize with time in the reaction medium to the corresponding *cis*-analogues (**14**), (**16**), and (**18**).

WITH the recent recognition of the first five indenobenzazepine alkaloids, lahorine (**1**), lahoramine (**2**),[1] fumarofine (**3**),[2] fumaritrine (**4**), and fumaritridine (**5**),[3] we were faced with the task of developing new synthetic routes to this unusual naturally occurring tetracyclic skeleton.†

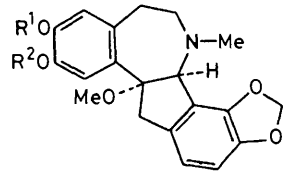
A particularly attractive route appeared to be through the known protopine (**7**),[4] derived from air oxidation of the readily available *N*-methyl-13-oxocanadinium salt (**6**).[5] Indeed, when a solution of (**7**) in potassium t-butoxide in t-butyl alcohol was subjected to sunlight for 7—8 h, a 40% yield of the *cis*-B/C-fused indenobenzazepine (**8**) was obtained.



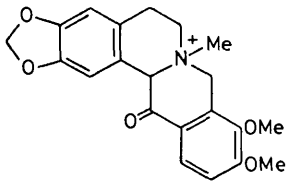
(1) $R^1 + R^2 = CH_2$
(2) $R^1 = R^2 = Me$



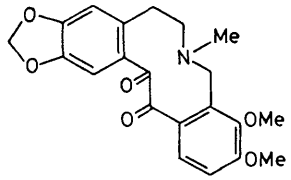
(3)



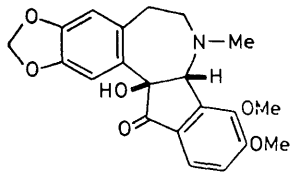
(4) $R^1 = R^2 = Me$
(5) $R^1 = Me$, $R^2 = H$



(6)



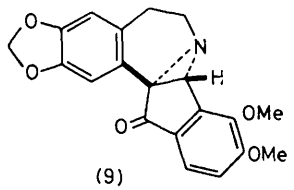
(7)



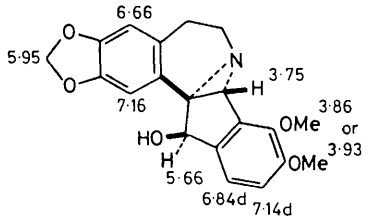
(8)

Within the indenobenzazepine alkaloids, the *cis*-B/C ring fusion is the thermodynamically more stable one,[2] and is actually encountered in fumarofine (**3**), fumaritrine (**4**), and fumaritridine (**5**). It was, nevertheless, of interest to develop a convenient method for the preparation of *trans*-B/C-fused indenobenzazepines since there is a possibility that alkaloids with this stereochemistry might be found in the future.

The oxo-aziridine (**9**), obtained by photoisomerization of berberinephenolbetaine,[6] was reduced with sodium borohydride in methanol. The major product was the alcohol (**10**), $C_{20}H_{19}NO_5$, m.p. 212—213 °C (EtOAc), formed by approach of the reagent from the less hindered side of the molecule. Significantly, however, the minor product proved to be the *trans*-B/C-fused indenobenzazepine (**11**), $C_{21}H_{23}NO_6$, m.p. 196—198 °C (EtOAc).[7]



(9)



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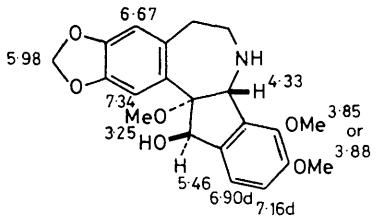
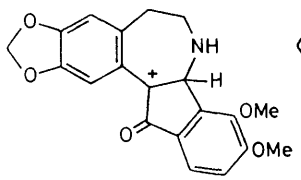
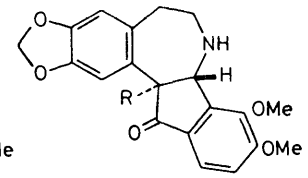


(11)

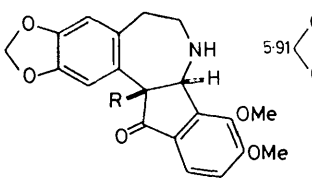
The finding that a *trans*-B/C-fused indenobenzazepine could be formed from the oxo-aziridine (**9**) induced us to develop this approach further. Treatment of (**9**) with hydrogen chloride in methanol for 8 h furnished a 60% yield of the *trans*-fused indenobenzazepine (**13**), $C_{21}H_{21}NO_6$, m.p. 179—180 °C (EtOAc), together with the *cis*-fused analogue (**14**) as the minor product (25%), $C_{21}H_{21}NO_6$, m.p.



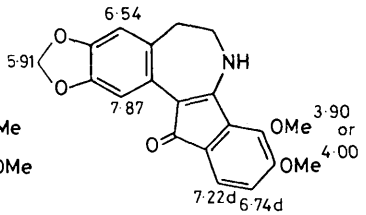
(12)



(13) R = OMe
(15) R = OH
(17) R = OAc



(14) R = OMe
(16) R = OH
(18) R = OAc



(19)

† Two other routes to the indenobenzazepines have been described: (a) from the rearrangement of spirobenzylisoquinolines leading to indenobenzazepines unsaturated at C(13)–C(14),[1-3,8] and (b) from the addition of formaldehyde to the oxo-aziridine (**9**), followed by cyanoborohydride reduction.[6]

185—187 °C (EtOAc). When the reaction was allowed to proceed for a longer time (16 h), the major product was the isomer (**14**), while (**13**) became a minor component. With an even longer time, only (**14**) could be detected, which could not be isomerized to (**13**). It is clear, therefore, that (**13**) is the kinetically controlled product, formed by *N*-protonation of (**9**) followed by cleavage of the critical N(7) to C(14) bond to form the carbonium ion (**12**) which at this stage is close enough in conformation to its aziridine precursor (**9**) to be immediately quenched by methanol to supply the *trans*-isomer (**13**). When set aside in hydrogen chloride in methanol, however, (**13**) reverts back to the cation (**12**), which is now completely planar and recombines with methanol to produce the thermodynamically favoured *cis*-isomer (**14**).

Similarly, treatment of the oxo-aziridine (**9**) with 5% hydrochloric acid led to the amorphous *trans*-indenobenzazepine (**15**) (51%), $C_{20}H_{19}NO_6$, and the amorphous analogue (**16**) (23%), $C_{20}H_{19}NO_6$, with the yield of (**16**) increasing with reaction time. Likewise, reaction of (**9**) with ammonium acetate in glacial acetic acid generated the *trans*-indenobenzazepine acetate (**17**) (54%), amorphous, $C_{22}H_{21}NO_7$, and the *cis*-acetate (**18**) (27%), amorphous, $C_{22}H_{21}NO_7$. As expected, the yield of the latter isomer increased with time.‡

Finally, a method was also found for the facile isomerization of the oxo-aziridine (**9**) into the amorphous enaminoketone (**19**), $C_{20}H_{17}NO_5$, λ_{max} (MeOH) 213, 242 sh, and 305 nm (log ϵ 4·15, 3·95, and 4·11), in 77% yield, using iodine in methylene dichloride at room temperature. Efficient methods are, therefore, now available for the preparation of indenobenzazepines incorporating either a *cis*- or a *trans*-B/C-fusion, or even a double bond between C(8) and C(14).§

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‡ The 200 MHz (Fourier transform; $CDCl_3$) n.m.r. chemical shifts for the new compounds where not indicated directly on the structures above are as follows: (**13**), δ 3·21 (3H, s), 3·91 and 3·95 (2 × 3H, s), 4·61 (1H, s), 5·96 (2H, s), 6·67 and 7·41 (2 × 1H, s), 7·64 and 7·01 (2 × 1H, d); (**14**), δ 3·31 (3H, s), 3·96 and 3·97 (2 × 3H, s), 4·42 (1H, s), 5·91 and 5·97 (2H, 2 × d, J_{gem} 1·5 Hz), 6·70 and 7·26 (2 × 1H, s), 7·06 and 7·63 (2 × 1H, d); (**15**), δ 3·91 and 3·97 (2 × 3H, s), 4·31 (1H, s), 6·67 and 7·43 (2 × 1H, s), 7·05 and 7·70 (2 × 1H, d); (**16**), δ 3·98 (6H, s), 4·47 (1H, s), 5·90 and 5·95 (2H, 2 × d, J_{gem} 1·2 Hz), 6·68 and 7·04 (2 × 1H, s), 7·09 and 7·66 (2 × 1H, d); (**17**), δ 2·30 (3H, s), 3·80 and 3·94 (2 × 3H, s), 4·82 (1H, s), 5·93 (2H, s), 6·70 and 7·40 (2 × 1H, s), 7·02 and 7·72 (2 × 1H, d); and (**18**), δ 2·13 (3H, s), 3·96 and 3·98 (2 × 3H, s), 4·80 (1H, s), 5·89 and 5·94 (2H, 2 × d, J_{gem} 1·5 Hz), 6·70 and 6·93 (2 × 1H, s), 7·07 and 7·66 (2 × 1H, d). The coupling constant between 11- and 12-H for the indenobenzazepines is always near 8·5 Hz. It will be noticed that in the *trans*-series [(**13**), (**15**), and (**17**)] the methylenedioxy-protons appear as a singlet, while the two methoxy-singlets are relatively well separated. In the *cis*-series [(**14**), (**16**), and (**18**)], on the other hand, the methylenedioxy-protons appear as an AB quartet, and the two methoxy-singlets are close together.

§ Elemental analyses are by mass spectroscopy. All synthetic compounds are racemates.

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