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A SHORT, EFFICIENT, SYNTHETIC PATHWAY TO THE 6,7,8,9-TETRAHYDRO-5H-DIBENZ[d,f]AZONINE SYSTEM

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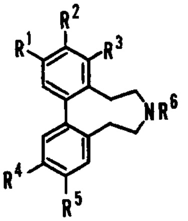
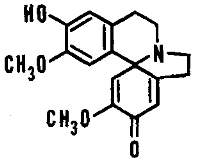
Summary: The intramolecular, nickel-promoted coupling of a bis[β-(o-iodophenyl)ethyl] amine produces a dibenzazonine of the type exemplified by several naturally occurring compounds and which serve as biosynthetic precursors of the Erythrina alkaloids.

The 6,7,8,9-tetrahydro-5H-dibenz[d,f]azonines are a class of alkaloids of which several members have been found in nature.[1] A typical example is protostephanine, 1, which possesses significant hypotensive activity.[1a] In addition to the importance of these compounds as potentially useful drugs for the treatment of hypertension, they are also important as both biosynthetic and synthetic precursors of the Erythrina alkaloids,[2] representatives of which are potent curare-like muscle relaxants.[3] As an example of a synthetic interconversion, 2 may be converted into erysodienone, 3, in 80% yield by treatment with potassium ferricyanide.[2] Therefore, the development of an efficient synthetic pathway to the dibenzazonines would also serve to provide a route to the Erythrina alkaloids. Routes to the former compounds have been reported previously,[4] but they are generally rather long and inefficient. For example, earlier workers devised what they described as a "practical" synthesis of 1, but the route consisted of seventeen steps![4a] We now wish to report the preliminary results of our investigation of a new, short, and efficient route to the dibenzazonine system.



1, $R^1=R^3=R^4=R^5=OCH_3$
$R^2=H$, $R^6=CH_3$
2, $R^2=R^6=OCH_3$,
$R^2=R^5=OH$, $R^3=R^6=H$
11, $R^2=R^5=OCH_3$, $R^1=R^3=R^4=H$, $R^6=CH_3$



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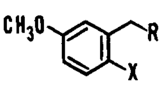
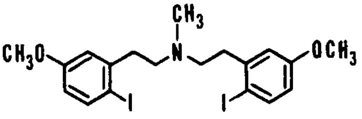


4, X=H, $R=CO_2H$
5, X=H, $R=CH_2OH$
6, X=I, $R=CH_2OH$
7, X=I, $R=CH_2OTs$
8, X=I, $R=CH_2NHCH_3$
9, X=I, $R=CH_2I$



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The iodotosylate, **7**, was prepared through use of the following three steps: (1) reduction of commercially available 3-methoxyphenylacetic acid, **4** (BH_3,[5] THF, 0°C, 97%), to produce the alcohol, **5**; (2) iodination (I_2, CF_3CO_2Ag,[6] $CHCl_3$, 89%) to produce the iodoalcohol, **6**; (3) tosylation (TsCl, pyridine, 0-25°C, 91%) to afford **7**. A portion of **7** was converted into the 2° amine, **8** (excess CH_3NH_2, ether, -13°C, 84%), and another portion was converted into the phenethyl iodide, **9** (NaI, acetone, reflux, 82%). Reaction of **8** and **9** (Na_2CO_3, CH_3CN, 89%) gave the 3° amine, **10**, which served as a substrate for an intramolecular aryl halide coupling reaction.[7] Of the reagents and conditions that were used for the coupling reaction, the best results were obtained by slow addition (0.5-2 h) of a 0.02 *M* solution of **10** in DMF to a 0.06 *M* solution of $Ni(PPh_3)_4$[7b] in DMF at 55°C. Under these conditions, the dibenzazonine, **11**, was obtained in 60% yield. The overall yield of **11** from the acid, **4**, is 35% by the six-step pathway proceeding through the phenethyl iodide, **9**. We are presently applying this route to the synthesis of several of the naturally occurring dibenzazonines and, ultimately, the *Erythrina* alkaloids.

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FOOTNOTES AND REFERENCES

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