ALTERNATIVE SYNTHESES OF (±)-EPI- AND (±)-DESETHYL-IBOGAMINE USING A DIELS-ALDER REACTION OF 1-BENZYL-2(1*H*)-PYRIDONE

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The Diels-Alder reaction of 1-benzyl-2(1*H*)-pyridone (1) with methyl acrylate (2) gave methyl 2-benzyl-3-oxo-2-azabicyclo-[2.2.2]oct-7-ene-6-*endo*-carboxylate (3) as a main product. Using this compound a short total synthesis of (±)-epi-ibogamine was achieved. (±)-Desethylibogamine was also synthesized formally from the Diels-Alder adduct (11) of 1 with maleic anhydride.

The Diels-Alder reaction of 1-methyl-2(1*H*)-pyridone[1] with methyl acrylate (2) and with acrylonitrile produced mainly the appropriate substituted isoquinuclidine derivatives which were easily accessible for a synthesis of iboga alkaloids. The further studies on the Diels-Alder reaction of 1-benzyl-2(1*H*)-pyridone (1) with 2 were continued and we wish to demonstrate herein the potential availability of a Diels-Alder reaction of 1 for the total syntheses of (±)-epi-ibogamine and (±)-desethylibogamine.

A mixture of 1 and 2 was heated at 135-140° for 2 weeks to give four kinds of the adducts, methyl 2-benzyl-3-oxo-2-azabicyclo[2.2.2]oct-7-ene-6-*endo*-carboxylate (3) [colorless needles, mp 86-87°, MS *m/e*: 271 (M^+), 17% yield] as a main product and three minor compounds, 4 (mp 99-100°, 0.8% yield), 5 (mp 109-110°, 1.4% yield), and 6 (mp 97-98°, 0.4% yield). The structures of these products were confirmed by their chemical properties (iodolactonization for the *endo*-isomers 3 and 5) and spectral analyses (MS, IR, NMR) compared with their 1-methyl derivatives which were unequivocally characterized previously[1] (Chart 1).

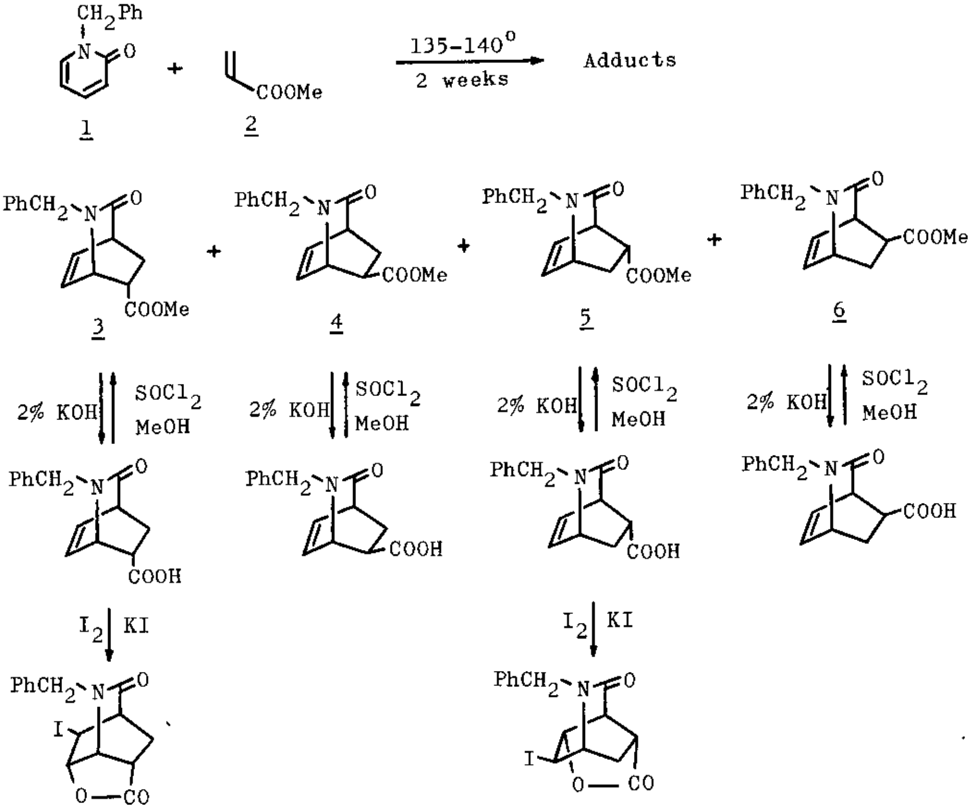

Chart 1

The main product (3) was reduced with LiAlH$_4$ to give the methylol (7) [MS *m/e*: 229 (M$^+$). methiodide; pale yellow prisms, mp 161-163°] in 80% yield. Tosylation (94% yield) of 7 followed by treatment with MeMgI and Li$_2$CuCl$_4$ (72% yield) gave the isoquinuclidine derivative (8) [MS *m/e*: 227 (M$^+$). methiodide; pale yellow prisms, mp 167-169°]. Treatment of 8 with 2-(3-indolyl)ethyl bromide gave the quaternary ammonium salt (9) (amorphous, 90% yield) and debenzylation of 9 with *n*-C$_3$H$_7$SLi and HMPA[2] afforded the indolylethyl compound (10) [colorless prisms, mp 95-97°, MS *m/e*: 280 (M$^+$)] in 33% yield. (±)-Epi-ibogamine was finally obtained by cyclization of 10 with (MeCN)$_2$PdCl$_2$-AgBF$_4$-Et$_3$N followed by NaBH$_4$ reduction[3] in 20% yield. The structure of (±)-epi-ibogamine obtained was confirmed by the following way; the infrared spectrum of the product (mp 192-195°) was superimposable on that of the authentic sample[4] (mp 194-196°) kindly provided by Professors Y. Ban and T. Wakamatsu[4]. The identity of both samples was further confirmed by the mixed melting point determination and retention time on HPLC [MeOH (100 ml)-AcOH (0.7 ml) solution containing H_3BO_3 (500 mg)] (Chart 2).

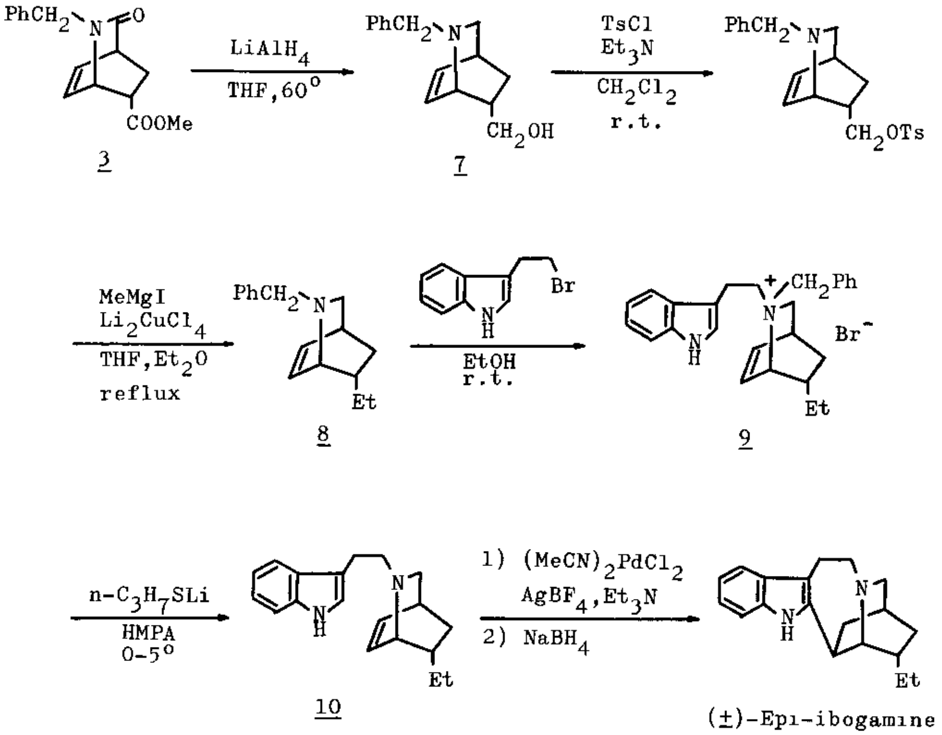

Chart 2

The Diels-Alder reaction of 1-benzyl-2(1H)-pyridone (1) with maleic anhydride under the same conditions for that of 1-methyl-2(1H)-pyridone[5] followed by hydrolysis gave the adduct (11) [colorless prisms, mp 168-170°, MS m/e: 283 (M^+-18)] in 41% yield. Catalytic reduction (99% yield) of 11 and subsequent decarboxylation with $Pb(OAc)_4$ afforded the olefin (12) [colorless needles, mp 80-82°, MS m/e: 213 (M^+)] in 43% yield. Reduction of 12 with $LiAlH_4$ gave the amine (13) [methiodide; colorless prisms, mp 174-175°(dec.)] in 90% yield. Treatment of 13 with 2-(indolyl)ethyl bromide gave the quaternary ammonium salt (14) (amorphous, 50% yield) and debenzylation of 14 with n-C_3H_7SLi and HMPA[2] afforded the indolylethyl compound (15) [colorless prisms, mp 128-130° (lit.[6] mp 118-120°), MS m/e: 252 (M^+), 7.4% yield] which had already been transformed into (±)-desethylibogamine by Trost and Genêt[6] (Chart 3).

Further investigation for the extension of these methods is now in progress.

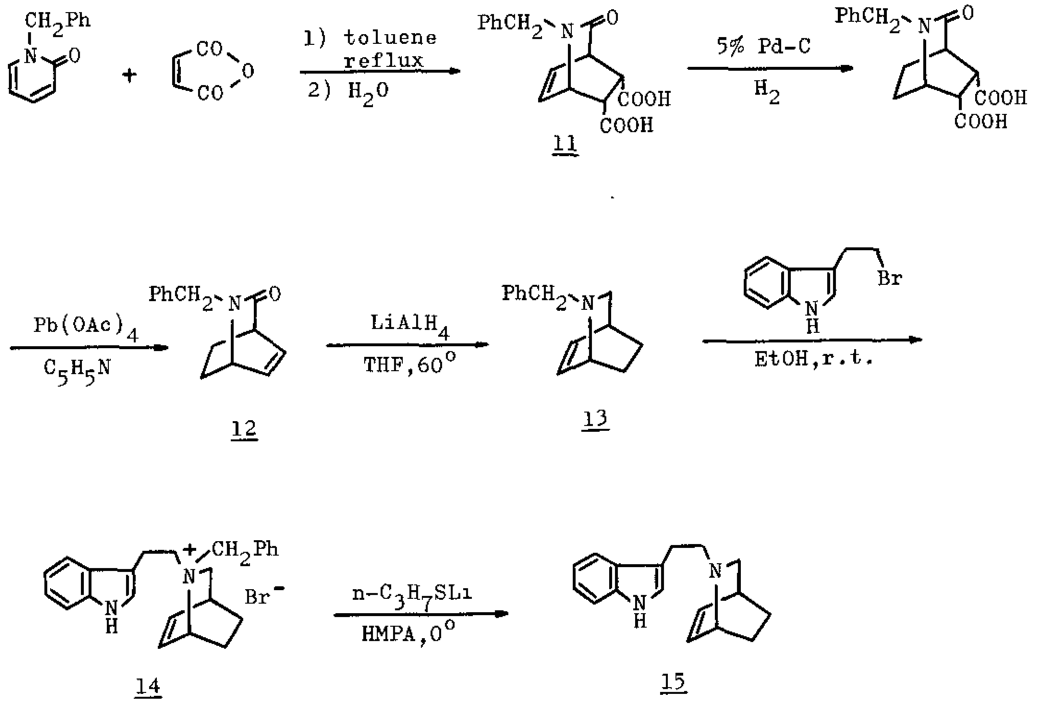

Chart 3

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