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INTRAMOLECULAR FRIEDEL-CRAFTS ALKYLATIONS. II[1]. AN EFFICIENT SYNTHESIS OF BIOLOGICALLY ACTIVE 1,2,3,4-TETRAHYDROISOQUINOLINES

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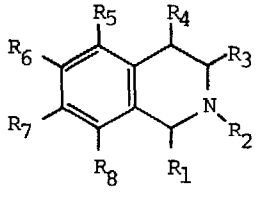
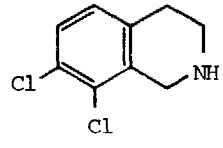
SUMMARY: A new synthesis of tetrahydroisoquinolines bearing electron withdrawing groups is presented. The scope and mechanism of the reaction are discussed. Many of these tetrahydroisoquinolines are potent inhibitors of the enzyme PNMT.

Compounds of the general type 1[2,3] are inhibitors of the enzyme phenylethanolamine N-methyltransferase (PNMT). PNMT catalyzes the final step in the biosynthesis of epinephrine, effecting the transfer of a methyl group from S-adenosylmethionine to the terminal nitrogen of norepinephrine. These compounds are of biological interest as potential therapeutic agents for disorders where specific control of adrenal epinephrine production might be beneficial[4]. Within this group of compounds, 7,8-dichloro-1,2,3,4-tetrahydroisoquinoline (2) is a potent, selective, reversible and long lasting inhibitor of PNMT in vivo.[5]



where: R_1, R_3, R_4 = Proton or C_1-C_2 alkyl group
R_2 = Proton or methyl group
R_5-R_8 = Proton or electron withdrawing groups

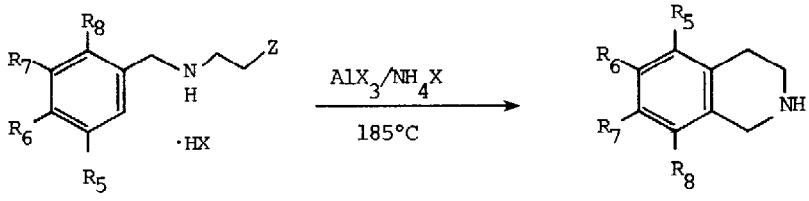
1



2

A variety of synthetic methods exist for the preparation of isoquinolines, [6-13] but they are either lengthy or produce poor to negative results when applied to the formation of 2. Although the Pomeranz-Fritsch reaction is capable of producing systems containing electron withdrawing groups in the desired substitution pattern, its usefulness is severely limited by the yields obtained. [10] A report by Deady et al.[14] claiming a new synthesis of relatively deactivated 1,2,3,4-tetrahydroisoquinolines was therefore of particular interest to us. In our hands, this method produced inconsistent results[15] and failed in application to the preparation of 2.

We now report a facile synthesis of 1,2,3,4-tetrahydroisoquinolines having electron withdrawing substituents.[16] This method offers several advantages: it is a simple, direct, 'one-



3 where: X = Halogen 4

R_5–R_8 = Proton or Halogen

Z = a. Hydroxyl

b. Halogen (usually the same as X)

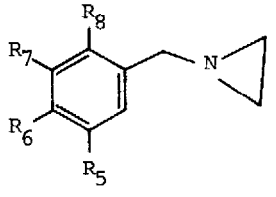
pot' preparation of tetrahydroisoquinolines in high yield, which is readily applied to large scale work. A typical procedure is as follows:[17] A mixture of 2-(2,3,-dichlorobenzylamino) 1-ethanol hydrochloride (2.0 gm, 7.8 mmol), ammonium chloride (0.3 gm, 5.7 mmol),[18] and aluminum chloride (2.0 gm, 15 mmol)[19] was added to a flask equipped with overhead stirrer and immersed in an oil bath preheated to 185°C.[20] Further portions of aluminum chloride were added at 40 min. (1.0 gm, 7.5 mmol) and 70 min. (2.0 gm, 15 mmol). After allowing the reaction to continue for 15 hrs. at 185°C,[21] the black melt was rapidly poured into a vigorously stirred slurry of ice–3N HCl (100 ml). The resulting homogeneous solution was then basified (pH 14) with 50% NaOH and extracted with diethyl ether (3x50 ml). The combined extracts were washed (sat. NaCl), dried ($MgSO_4$) and evaporated to an amber oil. The final product 2, isolated as the hydrochloride salt[22] (1.50 gm, 80%), was visualized as homogeneous by TLC analysis. The results of an elemental analysis of the tetrahydroisoquinoline agreed with theory, while both VPC and HPLC analyses demonstrated product purity to be >98% by weight. Further illustrative examples of this cyclization are shown in Table I.

Table I

Tetrahydroisoquinolines 4 synthesized from corresponding benzylamines 3

Z	X	R_5	R_6	R_7	R_8	Yield (wt.%)
OH	Cl	H	H	H	Cl	60
Cl	Cl	H	H	Ø	H	77
OH	Cl	H	H	H	Br	59
Cl	Cl	H	Cl	Cl	Cl	51
OH	Cl	H	Cl	Cl	H	41*

*Plus 22% of the 5,6 isomer from same starting material

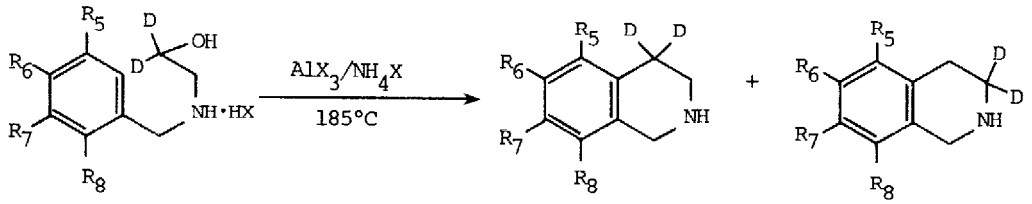


where: R_5–R_8 = Proton or Halogen

5

The mechanistic concepts governing Friedel-Crafts reactions are treated in detail by Olah.[23] Further interest in the mechanism of the above ring closure arises from a consideration of whether the tetrahydroisoquinolines 4 are produced directly from the amino-alcohols 3a, via conversion to the intermediate amino-halides 3b, or through formation of the aziridines 5.

The extent of participation of aziridine intermediates 5 was investigated by using the corresponding deuterium labelled compounds shown in Scheme I. When the labelled amino-alcohols



6 7 (100%) 8 (0%)

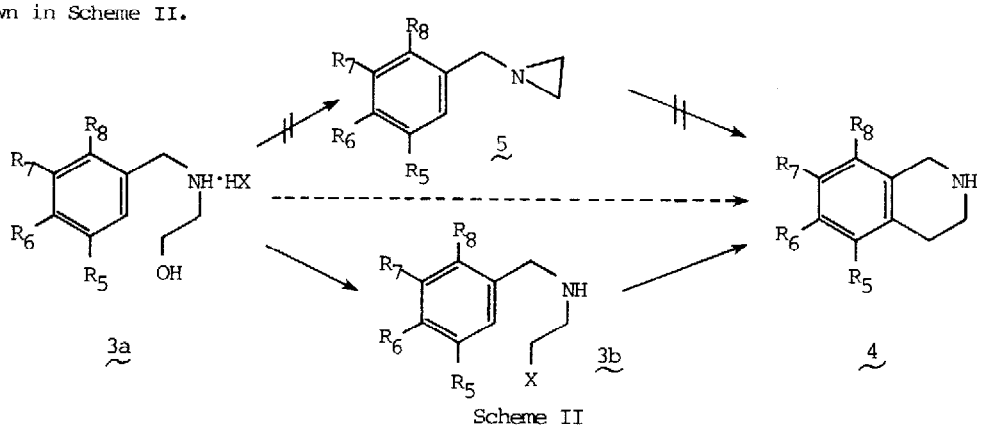
where: X = Halogen

R_5–R_8 = Proton or Halogen

Scheme I

6 were subjected to standard reaction conditions, NMR spectroscopy demonstrated the product to consist entirely of C-4 deuterated tetrahydroisoquinolines 7 with none of the C-3 deuterated compounds 8. Indeed, if aziridines were involved in this cyclization, one would have expected to find both products 7 and 8 present. Furthermore, when the aziridines 5 were prepared independently and subjected to the fusion conditions, only decomposition products were obtained.

The amino-halides 3b corresponding to starting materials 3a are observed during the course of the reaction via both TLC and HPLC analyses. Although the issue of direct formation of product remains unresolved, the conversion of amino-alcohols 3a to their corresponding amino-halides 3b appears to be an important step in producing tetrahydroisoquinolines 4 as shown in Scheme II.



3a 5 3b 4

Scheme II

This fusion technique can be used as a general procedure for the preparation of many isoquinolines of type 1 from N-(2-hydroxyethyl) benzylamines 3a or N-(2-haloethyl) benzylamines 3b. Extensions of this methodology leading to the formation of other heterocycles are currently under investigation.[24]

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REFERENCES AND NOTES

1. Part 1: C.B. Spainhour, Jr., W.L. Mendelson, S.S Jones, B.L. Lam and K.L. Wert, 179th National ACS Meeting, Houston, March 1980.
2. W.E. Bondinell et al., J. Med. Chem., 23, 0000 (1980).
3. R.G. Pendleton, SK&F Labs., personal communication.
4. C. Kaiser and R.G. Pendleton, Intra-Science Chem. Rept., Vol. 8, no. 4, (1974).
5. R.G. Pendleton et al., J. Pharmacol. & Exp. Ther., 197: 623-632, (1976).
6. F.W. Bergstrom, Chem. Rev., 35,217 (1944).
7. R.H.F. Manske, Chem. Rev., 30,145 (1942).
8. W. Gensler, in "Heterocyclic Compounds", Vol. 4, R.C. Elderfield, ed., 1952, pp. 344-490.
9. W.M. Whaley and T.R. Govindachari, in "Organic Reactions", Vol. 6, 1975, pp. 74-150, 151-190.
10. W. Gensler, in "Organic Reactions", Vol. 6, 1975, pp. 191-206.
11. P.A. Claret, in "Comprehensive Organic Chemistry", Vol. 4, "Heterocyclic Compounds", P.G. Sames, ed., 1979, pp. 205-232.
12. M. Gordon & D.E. Pearson, J. Org. Chem., 29, 329 (1964).
13. J. M. Bobbitt, in "Advances in Heterocyclic Chemistry", Vol. 15 A.R. Katritzky and A.J. Boulton, ed., 1973, pp. 99-136.
14. L.W. Deady, N. Pirzada and R.D. Topsom, Chem. Comm., 799 (1971).
15. R.D. Topsom, personal communication to W.L. Mendelson acknowledging that the experimental procedure reported in reference 14 is difficult to repeat.
16. B.L. Lam, W.L. Mendelson and C.B. Spainhour, Jr., U.S. Patent pending (1978).
17. For a discussion on the use of the double salt technique see: G.A. Olah, "Friedel-Crafts Chemistry", 1973, p. 262.
18. Alkali halides may be substituted for ammonium halides; omission of the inorganic salt results in only minimal changes in product yield and purity.
19. We found aluminum halides to be the most effective acidic catalysts for this ring closure. Other catalysts investigated were: BF_3, $SnCl_2$, SbF_3, $SbCl_5$, $SnCl_4$, $SnCl_4 \cdot 5H_2O$, $FeCl_3$, $TiCl_3$, $TiCl_4$, $ZnCl_2$, Cu_2Cl_2, H_2SO_4 and CH_3SO_3H/P_2O_5.
20. The easily stirred melt readily forms.
21. Optimal yields of the tetrahydroisoquinolines 4 are obtained from reactions carried out at temperatures between 180-200°C. The yields are poor outside this range; at temperatures >200°C undesired side products occur more frequently; at temperatures <180°C the reaction rates decrease. When reactions are run at temperatures below 160°C, starting materials are recovered nearly quantitatively.
22. A solution of diethyl ether-isopropanol (1:1) and crude 2 was acidified (pH2) with anhydrous hydrogen chloride.
23. G.A. Olah, "Friedel-Crafts Chemistry", 1973, pp. 393-475, 476-542.
24. W.L. Mendelson and C.B. Spainhour, Jr., manuscript in preparation.

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