A NEW SYNTHESIS OF 1-BENZYL-1,2,3,4-TETRAHYDROISOQUINOLINE

By L. W. DEADY,* N. H. PIRZADA,* R. D. TOPSOM,* and J. M. BOBBITT†

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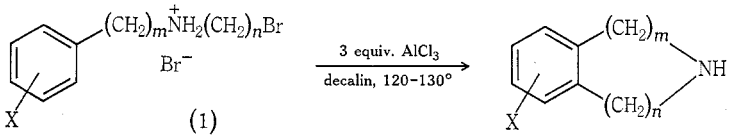
Abstract

The synthesis of *N*-(2-bromoethyl)-*N*-(1,2-diphenylethyl)ammonium bromide and its aluminium chloride catalysed decomposition to 1-benzyl-1,2,3,4-tetrahydroisoquinoline is described.

We have recently reported convenient preparations of tetrahydroquinolines[1] ($m = 0$, $n = 3$) and tetrahydroisoquinolines[2] ($m = 1$, $n = 2$) by the cyclization of compounds of type (1).



(1)

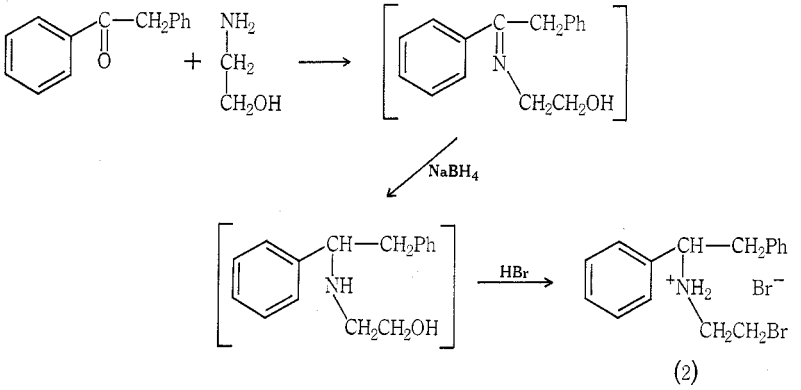
1-Benzyl-1,2,3,4-tetrahydroisoquinoline is the parent compound of an important class of alkaloids[3] and methods of synthesis of this system are of considerable interest. Normally, the system has been prepared by ring closure between C1 of the incipient isoquinoline and the aromatic ring, the so-called Bischler–Napieralski reaction,[4] although several new methods have been described and summarized.[5] In theory, the ring system can be prepared by closure of C4 (as an aldehyde or blocked aldehyde) to the aromatic ring by a variation of the Pomeranz–Fritsch synthesis,[5,6] but there are several difficulties with intramolecular ring closures[6] and only one successful synthesis has been reported.[7] In any case, such a synthesis results in oxygenation at C4 or some type of unsaturation in the isoquinoline ring. In this paper, we report a synthesis which is an extension of our previous work[2] and which gives the tetrahydroisoquinoline ring directly in reasonable yield.

Deoxybenzoin was used as the starting material in the synthesis of the required intermediate (2). Though the synthesis of (2) involved three steps it was experi-

* Organic Chemistry Department, La Trobe University, Bundoora, Vic. 3083.
† Chemistry Department, University of Connecticut, Storrs, Conn., U.S.A.

[1] Deady, L. W., Pirzada, N. H., and Topsom, R. D., *J. chem. Soc.* (*C*), 1971, 3719.
[2] Deady, L. W., Pirzada, N. H., and Topsom, R. D., *Chem. Commun.*, 1971, 799.
[3] Kametani, T., "The Chemistry of the Isoquinoline Alkaloids," (Kirokawa: Tokyo 1968).
[4] Whaley, W. M., and Govindachari, T. R., *Org. React.*, 1951, **6**, 74.
[5] Bobbitt, J. M., *Adv. heterocyc. Chem.*, 1973, **15**, in press.
[6] Gensler, W. J., *Org. React.*, 1951, **6**, 191.
[7] Vinot, N., and Quelet, R., *C. r. hebd. Séanc. Acad. Sci., Paris*, 1958, **246**, 1712.

mentally simple in that all were successively carried out in the one flask without isolation of either intermediate product. The overall yield in this sequence was 60%.



(2)

Decomposition of the intermediate (2) proceeded smoothly under the standard conditions and the 1-benzyltetrahydroisoquinoline was isolated as the trifluoroacetate salt in 32% yield. There was no evidence for the formation of a phenylazepine which would be produced by cyclization onto the other benzene ring; six-membered ring formation evidently predominates as expected.

This preparation holds some hope of having general applicability in the synthesis of this class of compounds in that there is at least one synthesis of deoxybenzoins which allows substituents in either aromatic ring to be independently varied.[8]

Experimental

N-(*2-Bromoethyl*)-N-(*1,2-diphenylethyl*)*ammonium Bromide*

Deoxybenzoin (10 g) was refluxed with aminoethanol (50 ml) for 4 hr. Excess aminoethanol was distilled off and the residue was dissolved in methanol (300 ml). A solution of sodium borohydride (14 g) in 1M sodium hydroxide (150 ml) was added dropwise with stirring and the temperature was maintained at less than 20°. Stirring was continued for 4 hr after completion of the addition and the methanol was then distilled off. Hydrobromic acid (200 ml, 48%) was added to the ice-cold residue and the mixture was then refluxed for 4 hr. The excess hydrobromic acid was removed by reduced pressure distillation. The residue solidified and was recrystallized from water to give the white crystalline product (11·8 g, 60%), m.p. 195–196° (Found: C, 50·0; H, 5·0; Br, 41·3. $C_{16}H_{18}Br_2N$ requires C, 50·0; H, 4·7; Br, 41·7%).

1-Benzyl-1,2,3,4-tetrahydroisoquinoline

A mixture of this salt (10 g), anhydrous aluminium chloride (10·5 g), and decalin (150 ml) was refluxed with stirring for 1 hr at 120–130°. Most of the decalin was decanted off and ice and concentrated hydrochloric acid were added to the oily residue. The mixture was extracted with ether, basified, and again extracted twice with ether.

These last ether extracts were dried, and the solvent was removed. The residue was dissolved in benzene (20 ml) and trifluoroacetic acid was added. The crude grey salt was collected and recrystallized from ethanol to give the pure trifluoroacetate, m.p. 160–161°, in 32% yield (Found: C, 64·1; H, 5·3; N, 4·2. $C_{18}H_{18}F_3NO_2$ requires C, 64·0; H, 5·3; N, 4·1%). The free base was isolated after treatment with aqueous sodium hydroxide. ν_{max} 3350br, 1605m, 1500s, 1455s, 1320m, 1125m, 755s, 735sh, 715sh, 700s cm^{-1}. The picrate had m.p. 164–165° (lit.[9] 166–167°).

[8] Krohnke, F., and Vogt, I., *Liebigs Ann.*, 1954, **589**, 26.

[9] Ban, Y., Yonemitsu, O., and Terashima, M., *Chem. pharm. Bull., Tokyo*, 1960, **8**, 183.