Notes

Friedel-Crafts Cyclization of Chloro-Substituted (Benzylamino)propyl Bromides. Formation of 4-Methyltetrahydroisoquinolines

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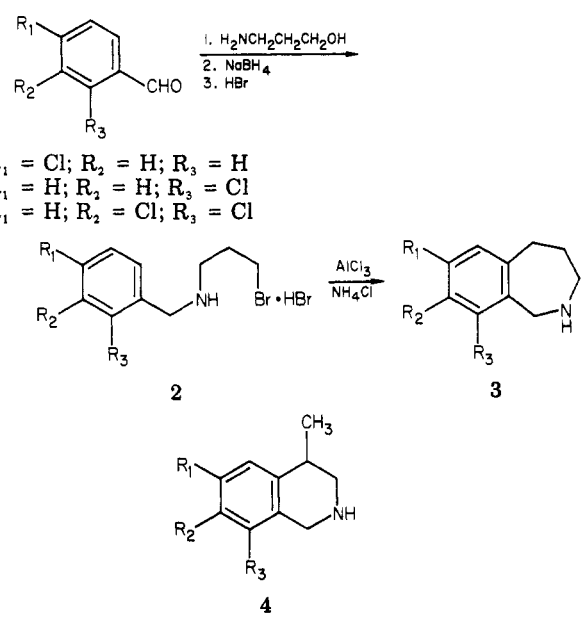
Tetrahydro-2-benzazepines are of interest as a result of their antihypertensive, adrenergic blocking, and cholinesterase inhibiting activity.[1] Although several methods of synthesis exist,[1] most of these are rather lengthy and/or not applicable to various substitution patterns of the aromatic ring. A report by Deady et al.[2] that Friedel–Crafts cyclization of (benzylamino)propyl bromide **2a** affords tetrahydro-2-benzazepine **3a** in good yield therefore appeared of particular significance. Utilization of this method for the preparation of **3b** and **3c**, inhibitors of the enzyme phenylethanolamine *N*-methyltransferase, was recently claimed.[3] Upon examining these reactions, however, we discovered that the major products from **2a–c**, which correspond to those reported to be **3a–c**, are in fact the isomeric 4-methyltetrahydroisoquinolines **4a–c** (Scheme I).

The (benzylamino)propyl bromides **2** were prepared by reductive amination of the appropriate benzaldehyde **1** with 3-amino-1-propanol, followed by treatment with hot 48% HBr. While the $AlCl_3$-catalyzed cyclization of **2** could be effected under Deady's conditions[2] in hot decalin, we found it more convenient to employ a fusion technique,[4] utilizing a melt of $AlCl_3$–NH_4Cl.[5] This technique afforded a similar product distribution to that obtained in decalin and also produced a cleaner, more rapid reaction. Following workup, the products were purified either through direct conversion to their HCl salts or by chromatography of the free base. All compounds were characterized as their HCl salts and, where appropriate, were converted to another salt for comparison with the literature melting point.[6] NMR spectral data, which were not reported in the earlier publications,[2,3] were quite definitive for the structural assignments (see Experimental Section). The 2-benzazepines **3** had distinct multiplets for the three contiguous methylene groups of the heteroring, whereas the 4-methyltetrahydroisoquinolines **4** displayed a doublet (J = 7 Hz) for the methyl group.

Cyclization of **2a** afforded as the major product (64%) **4a**, with lesser amounts (14%) of **3a** being formed. The latter product was identical with a sample prepared independently.[7] Reaction of **2b** gave 54% of **4b**; no **3b** was detected. Also produced was 14% of the isomeric tetrahydroisoquinoline **5**, apparently resulting from halide scrambling.[8] Finally, reaction of **2c** afforded **4c** in 72% yield. This product was decidedly different from an authentic sample of **3c** prepared by an unambiguous route.[7]

The observations reported here find precedent in the Friedel–Crafts literature. While isomerization of the initially formed carbonium ion in an intramolecular alkylation is less frequent than in the slower intermolecular reaction, it can occur with deactivated ring systems.[9,10]

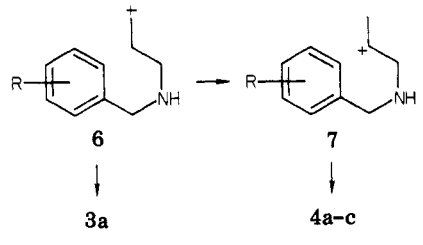
Scheme I



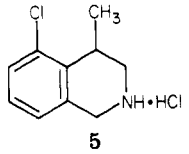
1a, R_1 = Cl; R_2 = H; R_3 = H
b, R_1 = H; R_2 = H; R_3 = Cl
c, R_1 = H; R_2 = Cl; R_3 = Cl

2 **3** **4**

Scheme II



6 **7** **3a** **4a–c**



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(1) S. Kasparek, *Adv. Heterocycl. Chem.*, 17, 45 (1974), and references therein.
(2) L. W. Deady, N. H. Pirzada, and R. D. Topsom, *J. Chem. Soc., Perkin Trans. 1*, 782 (1973).
(3) Belgian Patent 868471, Dec 27 (1978).
(4) G. A. Olah, Ed., "Friedel-Crafts and Related Relations", Vol. I, Interscience, New York, 1963, Chapter 4.
(5) For a description of the use of the fusion technique for the preparation of tetrahydroisoquinolines bearing electron-withdrawing substituents, see W. L. Mendelson, C. B. Spainhour, Jr., S. S. Jones, B. L. Lam, and K. L. Wert, *Tetrahedron Lett.*, in press.
(6) The melting points of the compounds reported here are consistently 8–9 °C higher than those found in ref 2. The melting points of the products reported in ref 3 are lower and broader than ours, probably due to the presence of isomeric impurities in their samples.
(7) W. E. Bondinell, Smith Kline & French Laboratories, personal communication.
(8) By coincidence, the melting points of the maleates of **4b**, **5**, and authentic **3b**[7] all correspond to that reported for **3b**.[3] Thus, we cannot say with certainty just which product the other group obtained. However, the preponderance of **4b** in the reaction mixture makes it likely that this is the compound they isolated.
(9) G. Baddeley and R. Williamson, *J. Chem. Soc.*, 4647 (1956).

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Thus, with **2a–c**, attack by **6** on the deactivated ring is slow relative to isomerization to **7**, resulting in the predominant formation of **4a–c** (Scheme II).

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 580 or Infracord spectrophotometer. NMR spectra were recorded on a Perkin-Elmer R-24 or a Varian FT-80 and are expressed in parts per million downfield from Me_4Si. Melting points were determined in evacuated, sealed capillaries on a Thomas-Hoover apparatus and are corrected. Elemental analyses were obtained from the Analytical and Physical Section of Smith Kline & French Laboratories.

Preparation of the (Benzylamino)propyl Bromides 2. A solution of 0.10 mol of the appropriate aldehyde **1** and 0.10 mol of 3-amino-1-propanol in 250 mL of EtOH was stirred under N_2 at ambient temperature for 20 h. Solid $NaBH_4$ (0.13 mol) was added over 1 h, and the mixture was stirred for another 4 h. Acid–base extractive workup then afforded the crude (benzylamino)propyl alcohol, which was cooled in ice and dissolved in 100 mL of 48% HBr. The mixture was distilled until ca. 50 mL had been collected and was then cooled in ice. The resulting solid was filtered and recrystallized from EtOH or MeOH–Et_2O, affording the following compounds.

3-[(4-Chlorobenzyl)amino]-1-bromopropane Hydrobromide (2a): 37%; mp 212–214 °C (lit.[2] mp 205–206 °C). Anal. Calcd for $C_{10}H_{13}BrClN\cdot HBr$: C, 34.97; H, 4.11; N, 4.08. Found: C, 35.03; H, 4.16; N, 4.16.

3-[(2-Chlorobenzyl)amino]-1-bromopropane Hydrobromide (2b): 70%; mp 128–129.5 °C (lit.[3] mp 128–130 °C). Anal. Calcd for $C_{10}H_{13}BrClN\cdot HBr$: C, 34.97; H, 4.11; N, 4.08; Br, 46.52; Cl, 10.32. Found: C, 34.69; H, 4.18; N, 4.11; Br, 46.17; Cl, 10.03.

3-[(2,3-Dichlorobenzyl)amino]-1-bromopropane Hydrobromide (2c): 72%; mp 157–158 °C. Anal. Calcd for $C_{10}H_{12}BrCl_2N\cdot HBr$: C, 31.78; H, 3.47; N, 3.71. Found: C, 31.81; H, 3.42; N, 3.74.

Cyclization of the (Benzylamino)propyl Bromides (2). A mixture of 10.0 mmol of the appropriate compound and 0.56 g (10.5 mmol) of NH_4Cl was immersed in a preheated oil bath at the indicated temperature. The $AlCl_3$ (6.67 g, 50.0 mmol) was added over 5–10 min, causing the mixture to liquefy with the evolution of gas. After 15 min, the homogeneous mixture was dissolved in 50 mL of ice–3 N HCl, cooled in ice, and basified with 40% NaOH. The product was extracted with Et_2O, and the extract was washed with brine, dried over $MgSO_4$, and evaporated. TLC and VPC analyses of the reaction of **2c** indicated the presence of a single major product, which was isolated directly via the HCl salt. **2a** and **2b** each afforded two major products, which were purified by medium-pressure liquid chromatography (ca. 10% MeOH–CH_2Cl_2 on silica gel) prior to conversion to their HCl salts.

Cyclization of **2a** at 160 °C gave **6-chloro-4-methyl-1,2,3,4-tetrahydroisoquinoline (4a)**, 1.17 g (64%). For the hydrochloride: mp 194.5–195.5 °C (EtOH–Et_2O); IR (KBr) 818, 836, 846 cm^{-1}; NMR (D_2O) 1.37 (d, 3, J = 7 Hz, C-4 CH_3), 2.95–3.7 (m, 3, C-3 H and C-4 H), 4.34 (s, 2, C-1 H), 7.05–7.45 (m, 3, aromatic). Anal. Calcd for $C_{10}H_{12}ClN\cdot HCl$: C, 55.06; H, 6.01; N, 6.42; Cl, 32.51. Found: C, 55.14; H, 6.01; N, 6.42; Cl, 32.17. For the picrate, mp 183–185 °C (MeOH) (lit.[2] mp 174–175 °C).

Also obtained from **2a** was **7-chloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine (3a)**, 0.26 g (14%). For the hydrochloride: mp 250–252 °C (EtOH–Et_2O); IR (KBr) 828 cm^{-1}; NMR (D_2O) 1.93 (m, 2, C-4 H), 2.97 (m, 2, C-5 H), 3.45 (m, 2, C-3 H), 4.34 (s, 2, C-1 H), 7.25 (m, 3, aromatic). Anal. Calcd for $C_{10}H_{12}ClN\cdot HCl$: C, 55.06; H, 6.01; N, 6.42; Cl, 32.51. Found: C, 54.81; H, 6.10; N, 6.24; Cl, 32.88. For the picrate, mp 193–196 °C (MeOH).

Cyclization of **2b** at 160 °C gave **8-chloro-4-methyl-1,2,3,4-tetrahydroisoquinoline (4b)**, 0.99 g (54%). For the hydrochloride: mp 178–179 °C (CH_3CN); IR (KBr) 785 cm^{-1}; NMR (D_2O) 1.36 (d, 3, J = 7 Hz, C-4 CH_3), 2.95–3.7 (m, 3, C-3 H and C-4 H), 4.38 (s, 2, C-1 H), 7.34 (s, 3, aromatic). Anal. Calcd for $C_{10}H_{12}ClN\cdot HCl$: C, 55.06; H, 6.01; N, 6.42; Cl, 32.51. Found: C, 55.40; H, 6.36; N, 6.56; Cl, 32.63. For the maleate, mp 140–141 °C (EtOH) (lit.[3] mp 130–133 °C).

Also obtained from **2b** was **5-chloro-4-methyl-1,2,3,4-tetrahydroisoquinoline (5)**, 0.25 g (14%). For the hydrochloride: mp 169–170 °C (CH_3CN); IR (KBr) 770, 782 cm^{-1}; NMR (D_2O) 1.38 (d, 3, J = 7 Hz, C-4 CH_3), 3.4–3.7 (m, 3, C-3 H and C-4 H), 4.38 (s, 2, C-1 H), 7.0–7.5 (ABC pattern, 3, J_{AB} = 7 Hz, J_{BC} = 7 Hz, J_{AC} = 2.5 Hz, aromatic). Anal. Calcd for $C_{10}H_{12}ClN\cdot HCl$: C, 55.06; H, 6.01; N, 6.42; Cl, 32.51. Found: C, 55.41; H, 6.06; N, 6.52; Cl, 32.60. For the maleate, mp 139–140 °C (EtOH–EtOAc).

Cyclization of **2c** at 170 °C gave **7,8-dichloro-4-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (4c)**: 1.81 g (72%), mp 201–202 °C. Recrystallization from EtOH afforded an analytical sample: mp 210.5–212 °C (lit.[3] mp 199-203 °C); IR (KBr) 834 cm^{-1}; NMR (D_2O) 1.34 (d, 3, J = 7 Hz, C-4 CH_3), 2.9–3.65 (m, 3, C-3 H and C-4 H), 4.38 (s, 2, C-1 H), 7.25 and 7.40 (AB pattern, 2, J = 8 Hz, aromatic). Anal. Calcd for $C_{10}H_{11}Cl_2N\cdot HCl$: C, 47.56; H, 4.79; N, 5.55. Found: C, 47.56; H, 4.69; N, 5.82.

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Registry No. **1a**, 104-88-1; **1b**, 89-98-5; **1c**, 6334-18-5; **2a**, 40584-09-6; **2b**, 69739-56-6; **2c**, 69739-60-2; **3a**·HCl, 69739-52-2; **3a** picrate, 40584-17-6; **4a**·HCl, 73037-80-6; **4a** picrate, 73037-82-8; **4b**·HCl, 73037-83-9; **4b** maleate, 73037-85-1; **4c**·HCl, 73037-86-2; **5**·HCl, 73037-87-3; **5** maleate, 73037-89-5; 3-amino-1-propanol, 156-87-6; 3-[(4-chlorobenzyl)amino]-1-hydroxypropane, 73037-90-8; 3-[(2-chlorobenzyl)amino]-1-hydroxypropane, 69739-55-5; 3-[(2,3-dichlorobenzyl)amino]-1-hydroxypropane, 73037-91-9.

(10) L. R. C. Barclay and E. C. Sanford, *Can. J. Chem.*, **46**, 3315 (1968).

Synthesis of (7-(Alkylthio)- and 7-(arylthio)cycloheptatriene)tricarbonyliron and -hexacarbonyldiiron Complexes

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Recently we have reported new methods for the functionalization of the cycloheptatriene skeleton starting from either tropone or tropenylium ions.[1] Perhaps the most striking result was that the treatment of tropone (**1**) with 1,2-ethanedithiol or 1,3-propanedithiol, under typical conditions for dithioketalization of ketones,[2] gave instead the dithiocycloheptatrienes **2**.[3]

This method could not be extended to simple thiols, such as methanethiol, which, in the case of **1** gave intractable mixtures.[4] Also, the use of zinc dichloride in diethyl ether as a catalyst proved not to be useful, because in the case of **1** and 1,2-ethanedithiol we obtained intractable mixtures.[5]

(1) F. Pietra, *Acc. Chem. Res.*, **12**, 132 (1979).
(2) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", Vol. 5, Wiley-Interscience, New York, 1975.
(3) M. Cavazza, G. Morganti, and F. Pietra, *Tetrahedron Lett.*, 2137 (1978).
(4) M. Cavazza, G. Morganti, and F. Pietra, *Recl. Trav. Chim. Pays-Bas*, **98**, 165 (1979).

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