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A Synthesis of Substituted 1,4-Dihydro-3(2*H*)-isoquinolones

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In the last few years several 1-spiro-3-isoquinolones, prepared by the condensation of cyclic ketones with phenylacetamide, have been reported in the literature (1a-c). Recently (1d), Brossi reported two methods of synthesis of 3-isoquinolones with other substituents in the 1-position. One of these methods utilized the condensation of benzaldehyde with the methylamide of homoveratric acid while the second consisted of the reaction of methylamine with 2-bromomethyl-4,5-dimethoxyphenylacetic ester. We now wish to describe the preparation of two 2-methyl-1,4-dihydro-1-phenyl-3(2*H*)-isoquinolones (Va,b) from the appropriately substituted benzhydrylamine derivatives, *via* an aryne synthesis.

The benzhydrylamines (IIa,b) were prepared by a Leuckart reaction from the corresponding benzophenones (Ia,b). Acetylation of IIa,b led to the amides (IIIa,b) which were then alkylated (sodium hydride and methyl iodide) to give the *N*-methyl derivatives (IVa,b).

Using the method that Bunnet and co-workers described for the synthesis of *N*-methyl oxindoles (2), compounds IVa,b were cyclized with potassium amide in liquid ammonia to give the desired isoquinolones

(Va,b) in yields of between 8 and 14%. Reduction of Va,b with lithium aluminum hydride gave the tetrahydroisoquinolines (VIa,b). Compound VIa was shown to have the same melting point as the known 1-phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (3).

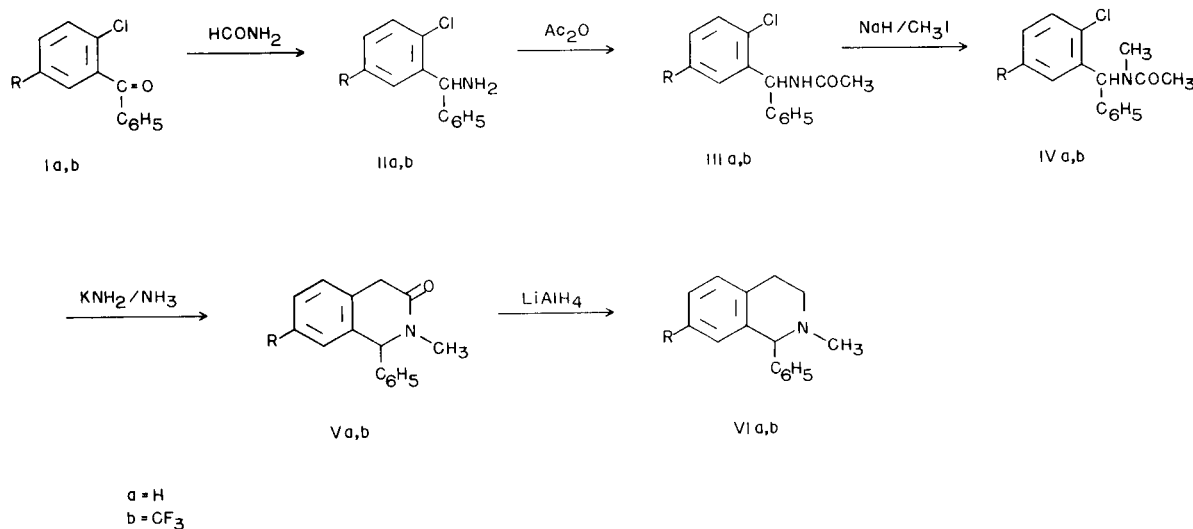
EXPERIMENTAL (4)

1-(2-Chlorophenyl)benzylamine Hydrochloride (IIa) and 1-(2-chloro-5-trifluoromethylphenyl)benzylamine Hydrochloride (IIb).

A mixture of 15 g. (0.069 mole) of *o*-chlorobenzophenone and 12.5 g. (0.276 mole) of formamide was stirred and heated at 195° for 8 hours, cooled to room temperature and treated with 60 ml. of ethanol and 60 ml. of 6*N* hydrochloric acid. The resulting solution was then heated under reflux for 5 hours. Ethanol was removed by distillation and the crude product was separated by filtration. The precipitate was washed thoroughly with benzene to remove unreacted chlorobenzophenone (7.6 g. recovered). Recrystallization of the residue from a methanol-ether mixture gave 7.9 g. (90%, based on starting material consumed) of the pure product as white prisms, m.p. 250-253°.

Anal. Calcd. for C₁₃H₁₂ClN·HCl: C, 61.43; H, 5.16. Found: C, 61.25; H, 5.38.

Using the same procedure the reaction of formamide and 2-chloro-5-trifluoromethylbenzophenone (Ib) (5) gave an 84% yield (based on starting material consumed) of IIb. The hydrochloride was recrystal-



lized from a mixture of methanol and ether to give the pure product as white needles, m.p. 191-200° dec.

Anal. Calcd. for $C_{14}H_{11}ClF_3N \cdot HCl$: C, 52.19; H, 3.75. Found: C, 52.40, 52.30; H, 3.72, 3.55.

N-[1-(2-Chlorophenyl)benzyl]acetamide (IIIa) and *N*-[1-(2-Chloro-5-trifluoromethylphenyl)benzyl]acetamide (IIIb).

A solution of 9.4 g. (0.0433 mole) of IIa in 30 ml. (0.324 mole) of acetic anhydride was treated with 5.0 g. of potassium acetate, and stirred at 60° for 30 minutes. The reaction mixture was cooled, poured onto ice, made basic with a 20% sodium carbonate solution, and then extracted with two 75 ml. portions of dichloromethane. The organic layers were combined, washed with saturated brine solution, dried over anhydrous sodium sulfate and evaporated to dryness. Recrystallization of the residue from a mixture of dichloromethane and hexane yielded 11 g. (98% of theory) of the product as white needles, m.p. 178-180°.

Anal. Calcd. for $C_{15}H_{14}ClNO$: C, 69.36; H, 5.43. Found: C, 69.18; H, 5.51.

Following the above procedure IIIb was obtained, which was recrystallized from a mixture of dichloromethane and cyclohexane to give the pure compound (90%) as white rods, m.p. 173-174°.

Anal. Calcd. for $C_{16}H_{13}ClF_3NO$: C, 58.64; H, 4.00. Found: C, 58.62; H, 3.93.

N-[1-(2-Chlorophenyl)benzyl]-*N*-methylacetamide (IVa) and *N*-[1-(2-Chloro-5-trifluoromethylphenyl)benzyl]-*N*-methylacetamide (IVb).

A solution of 7.0 g. (0.027 mole) of IIIa in 30 ml. of dry dimethylformamide was treated with 1.8 g. (0.0407 mole) of 53% sodium hydride, and stirred for 30 minutes at 5-10°. A solution of 7.6 g. (0.0542 mole) of methyl iodide in 10 ml. of dimethylformamide was added over a 10 minute period. The reaction mixture was stirred overnight at room temperature, and was then diluted with 100 ml. of dichloromethane. The solution was next washed with three 100 ml. portions of water, 50 ml. of saturated brine solution, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized from a mixture of dichloromethane and hexane to give 7.0 g. (93%) of IVa as white prisms, m.p. 113-114°.

Anal. Calcd. for $C_{18}H_{18}ClNO$: C, 70.19; H, 5.89. Found: C, 69.99; H, 5.83.

Compound IVb was prepared in the same manner and was recrystallized from a mixture of ether and petroleum ether to give the pure product (81%) as colorless prisms, m.p. 105-106°.

Anal. Calcd. for $C_{17}H_{15}ClF_3NO$: C, 59.74; H, 4.42. Found: C, 60.02; H, 4.32.

1,4-Dihydro-2-methyl-1-phenyl-3(2*H*)-isoquinolone (Va) and 1,4-Dihydro-2-methyl-1-phenyl-7-trifluoromethyl-3(2*H*)-isoquinolone (Vb).

A solution of potassium amide in liquid ammonia was prepared by dissolving 1.0 g. of potassium in 300 ml. of anhydrous liquid ammonia in the presence of ferric chloride. This solution was stirred for 90 minutes and was then added to a solution of 1.4 g. (0.005 mole) of IVa in 100 ml. of anhydrous liquid ammonia. The reaction mixture was stirred for 1 hour, and was then decomposed by the addition of ammonium chloride and 100 ml. of ether. The ammonia was evaporated and the ether solution was washed with water, saturated brine solution and then dried over anhydrous sodium sulfate. The ether was evaporated and the residual oil was dissolved in benzene and chromatographed over a column of alumina (50 g. of

"Woelm" Grade I neutral). Some of the by-products were removed by elution with ether, and the product was obtained from the ethyl acetate fraction. Recrystallization from a mixture of dichloromethane and hexane gave 0.1 g. (8% of theory) of Va as white prisms, m.p. 93-95°.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 81.12; H, 6.30.

Using the same procedure, 8 g. of IVb gave 1 g. (14%) of Vb. In this instance the product was recrystallized from a mixture of ether and hexane to give the pure compound as white plates, m.p. 120-123°.

Anal. Calcd. for $C_{17}H_{14}F_3NO$: C, 66.88; H, 4.62. Found: C, 66.80; H, 4.79.

2-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (VIa) and 2-Methyl-1-phenyl-7-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (VIb).

A solution of 0.6 g. (0.00253 mole) of Va in 20 ml. of dry ether was added dropwise to a solution of 0.16 g. (0.0043 mole) of lithium aluminum hydride in 50 ml. of dry ether (under nitrogen) and was heated under reflux for 3 hours. The reaction mixture was cooled in an ice bath, and a few drops of water were added, followed by enough saturated potassium bicarbonate solution to coagulate the mixture. The ether was filtered, and the filter cake was washed thoroughly with ether. The filtrates were combined and evaporated to dryness.

The residual oil was dissolved in petroleum ether (30-60°), filtered through 10 g. of alumina, using ethyl acetate as the eluent. Removal of the solvent and recrystallization of the product from aqueous ethanol gave 0.2 g. (36%) of theory of VIa as white rods, m.p. 70-72° (3).

Compound VIb was prepared from Vb in the same manner (37%) and was recrystallized from aqueous methanol as white needles melting at 55-60°. It was analyzed as the hydrochloride, which was recrystallized from a mixture of methanol and ether as white prisms, m.p. 193-202° dec.

Anal. Calcd. for $C_{17}H_{18}F_3N \cdot HCl$: C, 62.29; H, 5.23. Found: C, 62.61; H, 5.28.

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