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SYNTHESIS OF 1,2,3,3a,8,8a-HEXAHYDROINDENO[2,1-b]PYRROLE

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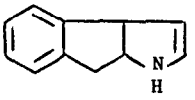
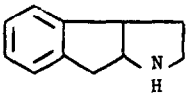
Although a synthesis of 1,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole (I) has been described,[1] a convenient approach to 1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole (II) has not been reported.[2] It is the purpose of this communication to outline a general synthetic route to this new class of heterocyclic compounds.



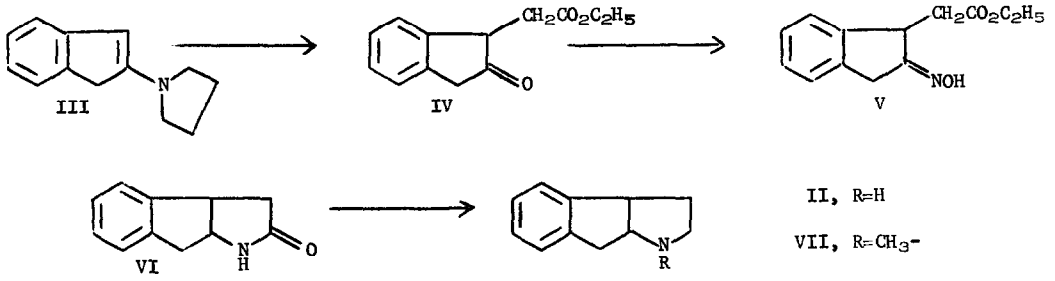
I



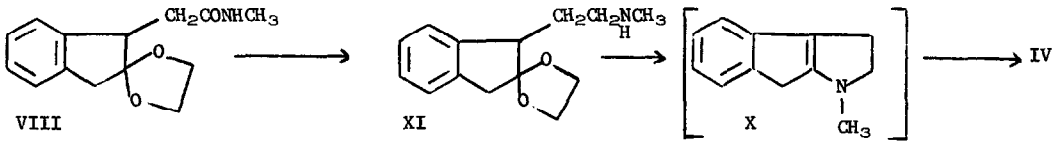
II

The route to II described here involves the construction of a pyrrolidine ring on an indane backbone as indicated in the following scheme. The pyrrolidine enamine II of 2-indanone[3] has been reported by Blomquist and Moriconi.[4] The enamine III was alkylated with ethyl bromoacetate in acetonitrile to provide a 63% yield after hydrolysis of ethyl indan-2-one-1-ylacetate (IV), b.p. 119-121°C at 0.05 mm; m.p. 47-48°C. The structure of IV was elucidated by the following physical data. IV: ν_{max}^{film} 1750, 1725, 750 cm^{-1}; m/e 218 (M^+); δ_{ppm}^{TMS} ($CDCl_3$) 1.15 (3H, t, J=7.5 Hz), 2.95 (2H, d, J=5.5 Hz), 3.55 (2H, s), 3.70 (1H, t, J=5.5 Hz), 4.05 (2H, q, J=7.5 Hz), 7.25 (4H, s). Treatment of the ketone IV with hydroxylamine hydrochloride in moist ether containing sodium bicarbonate provided an 85% yield of a mixture of the syn and anti-oximes V, m.p. 77-88°C; ν_{max}^{Nujol} 3200, 1725, 1675, 1175, 750 cm^{-1}. The mixture of oximes V was subjected to reductive cyclization over 5% Pd/C in acetic acid containing 10% by weight sulfuric acid to provide in 73% yield the lactam VI, m.p. 189°C. The structure was confirmed by the following physical data. VI: m/e 173 (M^+); ν_{max}^{Nujol} 3180 (N-H), 1680 (C=O), 745, 660 cm^{-1}; δ_{ppm}^{TMS} ($CDCl_3$) 2.7 (2H, m, benzylic), 3.1 (2H, m, CH_2-CO), 3.85 (1H, m, methine), 4.45 (1H, m, methine adjacent

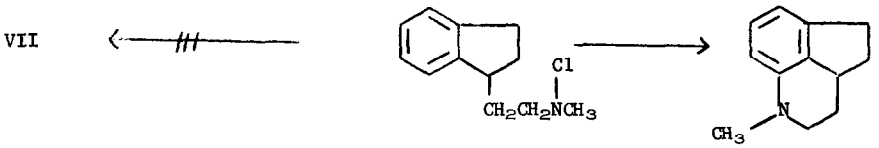
to N), 7.2 (4H, s, aromatic), 7.25 (1H, s, N-H). A cis ring junction in VI was suggested both by detailed analysis of the NMR spectrum and by the fact that the amino-ester intermediate was isolated and found to undergo facile, quantitative conversion to VI on sublimation. Reduction of the lactam VI with either lithium aluminum hydride in ether or diborane in tetrahydrofuran afforded 1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole (II), b.p. 88-90°C at 1.2 mm, the structure of which was supported by the following physical data. II: ν_{max}^{film} 740 cm^{-1}: δ_{ppm}^{TMS} (DCl, $CDCl_3$) 2.3-2.8 (2H, m, $\underline{CH_2}$-CH_2N), 3.1-3.9 (4H, m, CH_2N and benzylic methylene), 4.2 (1H, m, methine), 4.7 (1H, m, methine adjacent to N), 7.3 (4H, s, aromatic). The hydrochloride, m.p. 197-198°C, of II was prepared in the usual way. Treatment of II with ethyl chloroformate in triethylamine gave a urethane which on reduction with lithium aluminum hydride afforded the N-methyl analog VII, b.p. 65-66°C/0.3 mm; relative retention[5] 0.73 of II. The hydrochloride of VII crystallized from aqueous acetone as a dihydrate, m.p. 118-120°C. The structure of VII was supported by the following spectral data. VII: ν_{max}^{film} 755, 728 cm^{-1}; m/e 173.1174 (M^+); δ_{ppm}^{TMS} ($CDCl_3$) 1.6-2.4 (4H, m, $\underline{CH_2}$-CH_2N and benzylic methylene), 2.3 (3H, s, CH_3N), 2.9 (3H, m, CH_2N and methine), 3.7 (1H, m, methine adjacent to N), 7.15 (4H, s, aromatic).



An alternative synthetic approach[6] to VII also employing IV as the key intermediate was examined and found to be equally useful. The conversion of IV to its ethylene ketal was effected in the usual way. The ketal on treatment with lithium aluminum hydride-methylamine complex gave the amide VIII, m.p. 142-144°C; NMR δ_{ppm}^{TMS} ($CDCl_3$) 2.4 (2H, m), 2.75 (3H, d); 3.1 (2H, d), 3.7 (1H, t), 3.95 (4H, s), 6.0 (1H, broad), 7.1 (4H, s). Reduction of VIII with lithium aluminum hydride gave IX, b.p. 122-124°C/0.1 mm, NMR δ_{ppm}^{TMS} ($CDCl_3$) 2.4 (3H, s), 3.9 (4H, s), 7.1 (4H, s). Removal of the ketal protecting group from IX by treatment with dilute aqueous sulfuric acid gave a clear solution which was neutralized with sodium hydroxide to presumably provide the enamine intermediate X which was immediately extracted into ethyl acetate and hydrogenated over 5% Pd/C to provide IV in an overall yield of 63%.



The tertiary amine VII was of particular interest in view of the recent attempt[7] to synthesize VII through cyclization of N-chloro-N-methyl-β-(indan-1-yl)ethylamine XI under the conditions of the Hofmann-Löffler-Freytag reaction. Although the geometry of XI is such that δ-hydrogen abstraction by the intermediate aminium radical[8] could have led to VII, the preference of the intermediate for aromatic substitution apparently dominated the reaction thus leading to 1-methyl-1,2,3,3a-tetrahydrocyclopenta[de]quinoline (XII) as the sole product.[7] This result had also been observed in this laboratory. The experimental conditions employed in this laboratory apparently led to a purer sample of XII in considerably better yield than reported.[7] Photolysis (125 Hanovia immersion lamp) of a solution of 18.0 grams of XI in 190 ml of 80% sulfuric acid under a nitrogen atmosphere for 10 hours gave, after neutralization and ether extraction, 13.4 grams of XII, m.p. 53-54°C; relative retention[5] 1.42. The following spectral data supported the structure. XII: ν_{max}^{Nujol} 1610, 1500, 1320, 764, 722 cm^{-1}; m/e 173.1196 (M^+); δ_{ppm}^{TMS} ($CDCl_3$) 1.2-2.5 (4H, m), 2.6-3.1 (3H, m), 2.9 (3H, s), 3.1-3.5 (2H, m), 6.35 (1H, d, J=8Hz), 6.55 (1H, d, J=8 Hz), 7.0 (1H, t, J=8 Hz).



Although the NMR spectra clearly distinguished between the pyrrolidine VII and the tetrahydroquinoline XII, the mass spectra of VII and XII were surprisingly similar. Each amine exhibited an intense parent molecular ion (M^+) as well as intense ions at M^+-1 and M^+-15. Intense ions having the composition $C_{10}H_{10}N$, $C_{10}H_9$ and C_9H_7 were also observed in each spectrum. The spectrum of VII however contained a very intense ion at m/e 82.0652 (C_5H_8N) which was not found in the spectrum of XII. The full details of these fragmentation patterns as well as the chemistry of this new class of heterocyclic compounds will appear in a full publication.

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