Indole[3,2 g]indolizidines via Sodium Borohydride Reduction of Indolic Imides

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Acid-controlled sodium borohydride reduction of imides followed by cyclisation of the carbinol lactams formed affords the title compounds in good yields.

A recent communication in this journal on the possible application of the reductive cyclisation of imides as an attractive method for the synthesis of alkaloidal intermediates contained only negative results. Since we had advocated previously the great synthetic potential of this new method we were highly surprised to learn of the unexpected difficulties associated with it. Herein we want to describe the synthesis of a number of indole[3,2 g]-indolizidines in order to show once more the general applicability of the imide reduction method in the construction of heterocycles and also to comment on its apparent failure.

N-succinimide tryptamine (1) was reduced with sodium borohydride under pH-controlled conditions and the resulting hydroxylactam converted directly by refluxing with HCl dil into the indolizinone (3) in 86% yield. Similarly the N-glutarimido tryptamine (2) was reduced and cyclized to quinolizidone (4) in 56% yield in a single experiment.

The imide 5, prepared from tryptamine and cis-cyclohexene-1,2-dicarboxylic anhydride in 50% yield, m.p. 144-146 °C, was reduced with sodium borohydride/H2O and the resulting hydroxylactam cyclized directly by refluxing with HCl dil to the indolizinone (7) m.p. 228-235 °C dec (ethyl acetate), overall yield 90%. The substance was characterized by its lactam absorption at 1655 cm⁻¹ in the infrared, by major peaks in its mass spectrum at 278 (100%) M⁺ 237 (54%), 224 and 223 (55%) and by its 1H NMR spectrum (DMSO-d₆): δ 4.25 (d, J = 12 Hz) H₇; 4.55 (s) H₂; 5.88 (s, 2H) H₃. Analogously the imide 6, prepared from tryptamine and cis-1,2-cyclohexene dicarboxylic anhydride in 50% yield, m.p. 152-154 °C, was reduced and cyclized to 8 in 69% yield, m.p. 230 °C dec (acetone): IR νmax (KBr) 1655 cm⁻¹, mass: 280 (100%) M⁺ 279 (91%), 170 (22%), 169 (45%); 1H NMR (DMSO-d₆): δ 4.28 (d, J = 12 Hz) H₇; 4.60 (s, 1H) H₃. From the value of W1/2 = 9 Hz of the H₁₃B protons a trans relationship between H₁₃B and H₁₃S is assumed.

Obviously the aforementioned cyclisations have to proceed via the carbinol lactam. Since the target compounds were most conveniently prepared via a "one-pot" procedure no attempts were made to isolate and characterize the intermediate lactams. However, as a proof for the formation of the hydroxylactam the latter compound was isolated and characterized in the N-phthalimido series. Thus upon NaBH₄/H⁺ reduction of 9 and "base work-up" the carbinol lactam 10 was obtained in 86% yield, m.p. 179-182 °C (EtOH-Et₂O) IR νmax (KBr) 3300 (OH); 1660 (C=O) cm⁻¹, 1H NMR (DMSO-d₆): δ 3.04 (t, 2H, ArCH₂), 3.95-4.50 (m, 2H, NCH₃) 5.84 (d, 1H, CHOH), 6.63 (d, 1H, CHO);. The compound also showed a satisfactory microanalysis. Cyclisation of 10 by reflux in HCl dil afforded indolizinone 11, m.p. 214 to 230 °C in quantitative yield. The latter compound could also be obtained in a "one-pot" procedure, yield 91%.

Although the aforesaid reduction procedure is experimentally very simple two conditions have to be rigorously fulfilled in order to achieve the desired goal: i) addition of HCl dil at regular time intervals ii) maintenance of a satisfactory low temperature in order to prevent unwanted ring opening and overreduction. Most likely the latter circumstance has not been adequately controlled in the work of ATTA-UR-RAHMAN and the general applicability of the imide reduction method therefore seems unaffected.

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1 Part of the Ph. D. dissertation of J. C. HUBERT, University of Amsterdam [1974].