Reduction of Indolic Imides with Sodium Borohydride†

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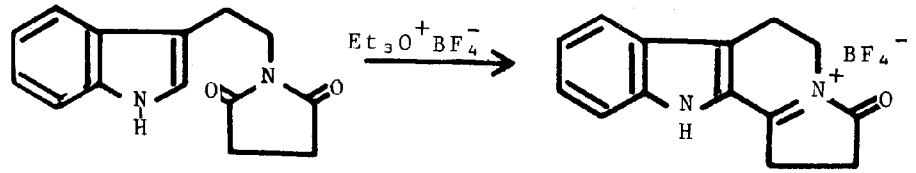
(Received 9th November, 1978)

Summary: The reduction of imides with sodium borohydride affords ring cleaved products.

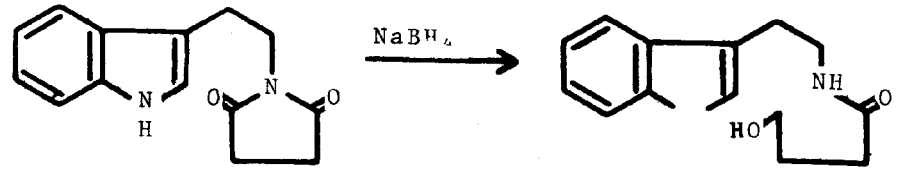
We have previously described[1] a new procedure for the cyclization of the imide(1) using triethyloxonium tetraflouroborate to the corresponding indole (3.2g) indolizine derivative(2) in high yields. Conventional procedures had earlier failed to effect such a cyclization[2].

It was reported by Speckamp and co-workers[3,4] that imides can be reduced with $NaBH_4$ to afford the corresponding carbinol lactams. Since the reaction appeared to have considerable potential in the synthesis of indole alkaloids, we decided to investigate it further by reducing indolic imides with $NaBH_4$ under buffered pH controlled conditions[3]. When N-succinimidotryptamine (3) was treated with various amounts of $NaBH_4$ under buffered pH controlled conditions it was found to be converted in high yields to a slower moving product which was identified as the amide alcohol (4) and crystallized readily from ethanol, m.p. 68°C. The substance obtained had a normal indolic ultraviolet spectrum and showed the amide carbonyl absorption at 1630 cm^{-1}. The mass spectrum afforded the molecular ion at m/e = 246 and other major peacks at m/e = 228, 200, 143, 130 and 103. The NMR spectrum was in accordance with the expected structure (4). No carbinol lactam (5) was detectable in the reaction mixture. When the same reduction was carried out in absolute ethanol instead of the burfered medium the amide ester (6) was also formed in addition to the amide alcohol (4), the latter being the major product.

N-Glutarimidotryptamine (7) when similarly reduced with $NaBH_4$ under pH controlled condition afforded a new slower moving product which also crystallized readily from ethanol, m.p. 68°C. The product obtained had a normal indolic U.V. and showed the amide carbonyl absorption at 1632 cm^{-1}. The mass spectrum afforded the molecular ion at m/e = 260 with other major peaks appearing at m/e = 240, 160, 143, 136 and 103. The NMR spectrum was in agreement with the

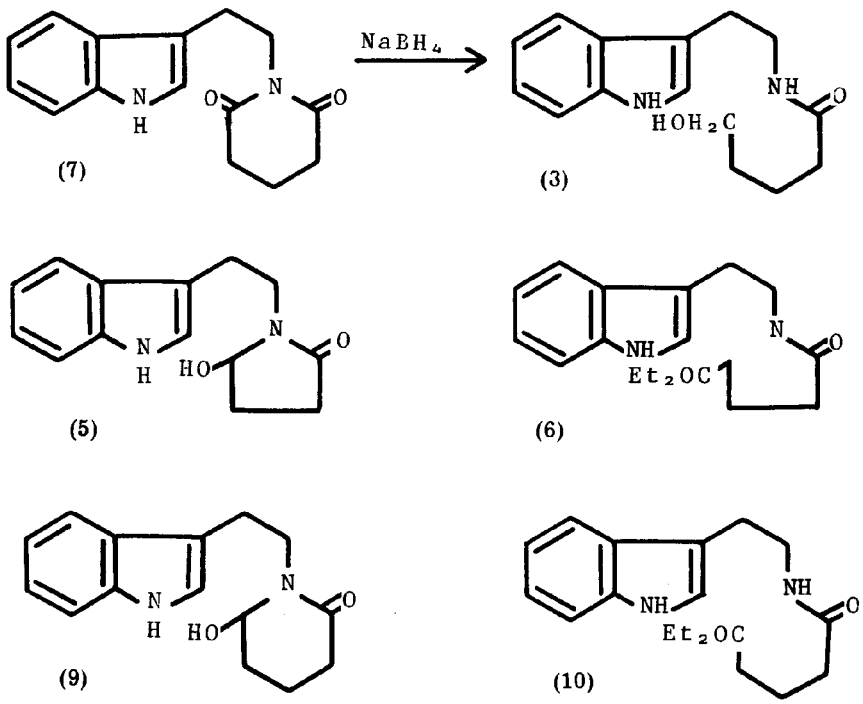


(1) (2)



(3) (4)

†Published as a short communication in *Zeitschrift fuer Naturforschung*, 31b, 287 (1976).



expected structure (8). No carbinol lactam (9) was detectable in the reaction mixture. When similar reduction was carried out in absolute ethanol instead of buffered medium a minor faster moving product was formed which was also found to be indolic and afforded the molecular ion at m/e = 302 as expected for the amide ester (10).

N-Phthalimidotryptamine (11) was also subjected to reduction with varying quantities of $NaBH_4$ in buffered media. It was found to be converted quantitatively to a new slower running material, m.p. 130°C. Structure (12) was assigned to the product based on its indolic U.V., amide absorption at 1632 cm^{-1} and mass spectrum (M^+ = 294, major peaks at m/e = 276, 200, 188, 143, 105 and 103). When the same reduction was repeated in absolute ethanol instead of the buffered medium, no amide ester was found to be formed.

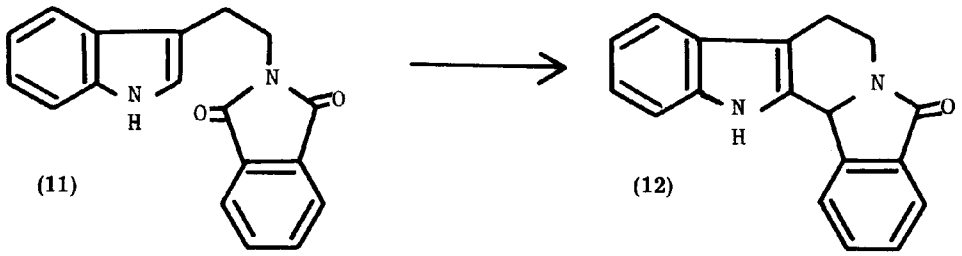
It is evident from these experiments that when imides are reduced with $NaBH_4$, the predominant tendency is for ring opening to occur. This observation is in agreement with the results of other workers[5-8] who have observed similar cleavages of imides. Since many of the substances examined by Speckamp and co-workers[4,9] possessed substituents α-to the imide carbonyl group, it is possible that the presence of such substituents results in sufficient ring stabilization so as to afford significant quantities of the intermediate hydroxy-lactams. Subsequent reports[10-12] of the formation of α-hydroxy lactams from cyclic imides all involve the reduction with sodium borohydride under acid conditions rather than buffered neutral solutions. The ring-opening of indolic imides appears to have significant possibilities of application in the syntheses of indole alkaloids.

Experimental

The infra-red spectra were recorded on a Unicam SP-200 I.R. spectrometer. The ultra violet spectra were recorded on a Unicam SP-800 U.V. spectrometer. The N.M.R. spectra were recorded on a JEOL PMX-60 spectrometer. The mass spectra were recorded on VG-Micromass MM-12 mass spectrometer.

Amide Alcohol (4)

N-Succinimidotryptamine (3) (500 mg., 0.002 mole) was dissolved in warm ethanol (40 ml). Then buffered aqueous solution, (pH 7.6, 25 ml, stock solution made by mixing 42.8 ml of 0.1N NaOH 50 ml of 0.1M KH_2PO_4 and 7.2 ml of H_2O) was added followed by the addition



(11) (12)

of $NaBH_4$ (462 mg., 0.014 mole) and the reaction was carried out at room temperature (27°C). The reaction was worked up after 2 hours when t.l.c. revealed the formation of a new slower moving substance. The undissolved $NaBH_4$ was filtered off from the reaction mixture and the filterate was evaporated under reduced pressure. The residue was partitioned between water (60 ml) and ethyl acetate (60 ml). The ethyl acetate layer was first washed with 0.1N sodium carbonate solution (20 ml) and then with water (50 ml). The ethyl acetate layer was then dried with anhydrous sodium sulphate, filtered and then evaporated to afford a white crystalline product. Recrystallization from hot ethanol afforded the pure amide alcohol (4), m.p. 68°C, (45 mg., 90% yield); U.V. spectrum: typically indolic, λ max = 225, 280, 290, λ min = 242, 285; IR spectrum: 1630 cm^{-1} (C = O stretching); mass spectrum: M^+ = 246 other major peaks are at m/e = 228, 200, 143, 130, and 103; NMR spectrum: δ 6.9-7.9 (4-H, aromatic), δ 4.43 (CH_2OH).

Amide ester (6)

N-Succinimidotryptamine (3) (100 mg., 0.0004 mole) was dissolved in warm ethanol (12 ml), then $NaBH_4$ (52 mg., 0.0016 mole) was added to the reaction mixture. The reaction mixture was allowed to stand at room temperature (29°C) for two hours. The reaction was then worked up and t.l.c. revealed the formation of two slow moving substances, the slower of the two being the major one. Undissolved $NaBH_4$ was filtered off from the reaction mixture and the filterate was evaporated under reduced pressure. The residue was partitioned between water (30 ml) and ethyl acetate (30 ml). The ethyl acetate layer was dried with anhydrous sodium sulphate and evaporated under reduced pressure. The two products were isolated through preparative t.l.c. the one corresponding to the amide alcohol (4) being formed in 90% yield. The minor faster running material which was obtained as a white crystalline product, was identified as the amide ester (6) (12 mg, 10% yield); U.V. spectrum: typically indolic, λ max = 225, 280, 291, λ min = 242, 285; IR spectrum: 1712 cm^{-1} and 1632 cm^{-1} (C = O stretching); mass spectrum: M^+ = 288, other peaks at m/e 243, 266, 169, 159.

Amide Alcohol (8)

N-Glutarimidotryptamine (7) (500 mg., 0.002 mole) was dissolved in warm ethanol (40 ml), then buffered aqueous solution (pH 7.6, 25 ml from stock solution made by mixing 42.8 ml of 0.1N NaoH, 50 ml of 0.1M KH_2PO_4 and 7.2 ml of water) was added, followed by the addition of $NaBH_4$ (437 mg., 0.0137 mole). The reaction was carried out at 27°C. The reaction was worked up after 2 hours when t.l.c. revealed the formation of a new slower moving substance. The undissolved $NaBH_4$ was filtered off from the reaction mixture and the filterate was evaporated under reduced pressure. The residue was partitioned between water (60 ml) and ethyl acetate (60 ml). The ethyl acetate layer was first washed with 0.1N sodium carbonate solution (20 ml) and then with water (50 ml). The ethyl acetate layer was then dried with anhydrous sodium sulphate filtered and then evaporated to afford a white crystalline product. Recrystallization from hot ethanol afforded the pure amide alcohol (8) (462 mg., 91% yield); m.p. 68°C; U.V. spectrum: typically indolic, λ max = 225, 280, 291, λ min = 242, 285; IR spectrum: 1632 cm^{-1} (C = O stretching) mass spectrum: M^+ = 260, other major peaks are at m/e = 240, 160, 143, 130 and 103; NMR spectrum: δ 7.0-7.9 (4 H, aromatic), δ 4.43 (CH_2OH).

Amide ester (10)

N-Glutarimidotryptamine (100 mg., 0.0004 mole) was dissolved in warm ethanol (12 ml), then $NaBH_4$ (50 mg., 0.0015 mole) was added to the reaction mixture. The reaction was carried out at 29°C for 2 hours in the absence of buffered media. The reaction was worked up and t.l.c. revealed the formation of two slow moving

substances. The slower of the two corresponded to the amide alcohol (8) while the faster moving was identified as amide ester (10). The slower moving material was found to be the major one Undissolved $NaBH_4$ was filtered off from the reaction mixture and the filterate was evaporated under reduced pressure. The residue was partitioned between water (30 ml) and ethyl acetate (30 ml). The ethyl acetate layer was dried with anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The two substances were isolated through preparative t.l.c. The faster moving amide ester was isolated in low yields. (10 mg., 9% yields), m.p. 90°C; U.V. spectrum: typically indolic, λ max = 225, 280, 291, λ min = 242, 285; IR spectrum: 1712 cm^{-1} and 1632 cm^{-1} (C = O stretching); mass spectrum: M^+ = 302 and other major peaks at m/e = 257, 242, 160, and 143.

Amide Alcohol (12)

N-Phthalimidotryptamine (11) (1g., 0.0034 mole) was dissolved in warm ethanol (80 ml). Buffered aqueous solution (pH 7.6, 25 ml, stock solution made by mixing 42.8 ml of 0.1N NaOH, and 50 ml 0.1M KH_2PO_4 and 7.2 ml of water) was added followed by the addition of $NaBH_4$ (770 mg., 0.024 mole). The reaction was carried out at 29°C for 2 hours when t.l.c. revealed the formation of a new slower moving substance. Undissolved $NaBH_4$ was filtered off from the reaction mixture and the filterate was evaporated under reduced pressure. The residue was partitioned between water (100 ml) and ethyl acetate (100 ml). The ethyl acetate layer was washed first with 0.1N sodium carbonate solution (20 ml) and then with water (50 ml). The ethyl acetate layer was then dried with anhydrous sodium sulphate, filtered and evaporated to afford a white crystalline product, (999.4 mg., 98.6% yield); m.p. 130°C; U.V. spectrum: typically indolic, λ max = 225, 280, 291, λ min = 242, 285; IR spectrum: 1632 cm^{-1} (C = O stretching); mass spectrum: M^+ = 294 and other major peaks at m/e = 276, 188, 160, 143, 105 and 103; NMR spectrum: δ 6.9-7.7 (8 protons, aromatic), δ 4.66 (2 protons, CH_2OH).

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