

SOME NEW DERIVATIVES OF TETRAHYDROHARMINE

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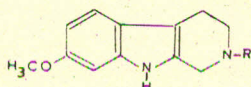
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A study of von Braun BrCN reaction has been carried out on tetrahydroharmine. As an extension of this reaction, the cyano derivative thereby formed has yielded on mild hydrolysis a product, the structure of which has been established through chemical and spectral evidence as *N*-amido tetrahydroharmine.

INTRODUCTION

In continuation of studies in structure and activity relationship in indole alkaloids, work has been extended to another indole base namely tetrahydroharmine. The base is the reduction product of harmine and harmaline (harmidine) which together form the principle alkaloidal factor of the seeds of *Peganum harmala*. In the present work attempts have been made to prepare some physiologically important synthetic analogues of tetrahydroharmine through Von Braun cyanogen bromide reaction. These studies have resulted in the preparation of the following new derivatives.



- (1) Tetrahydroharmine, R=(H)
- (2) *N*-cyano tetrahydroharmine R = (C≡N)
- (3) *N*-amido tetrahydroharmine R = (C(=O)-NH₂)
- (4) (*N,N*-dimethyl) amido tetrahydroharmine
R = (C(=O)-N(CH₂)₂)
- (5) (*N*-acetyl) amido tetrahydroharmine
R = (C(=O)-NH-C(=O)-CH₃)
- (6) (*N*-benzoyl) amido tetrahydroharmine
R = (C(=O)-NH-C(=O)-C₆H₅)
- (7) *N*-amido tetrahydroharmine sulphonic acid.

The present paper deals with the preparation and characterization of these products.

Tetrahydroharmine was treated with cyanogenbromide freshly prepared by the method of Scholl [1]. The reactants were brought together in chloroform solution and stirred at 5° for about an hour. On working up the

reaction product according to the method described in the experimental, *N*-cyano tetrahydroharmine was obtained as beautiful, pale yellow prismatic plates which melted at 280° and analyzed for C₁₄H₁₅N₃O (M⁺ 241). The yield was 70%. The *N*-amido derivative was prepared from *N*-cyano tetrahydroharmine through partial hydrolysis. The hydrolysis of *N*-cyano tetrahydroharmine presented great difficulties due to formation of tarry materials when the reaction was carried out with normal reagents like alcoholic and aqueous H₂SO₄ and HCl. Partial hydrolysis was subsequently achieved in basic medium by using 10% NaOH in the presence of hydrogen peroxide. The reaction product was worked up according to the procedure described in the experimental to yield colourless shining needles of *N*-amido tetrahydroharmine which melted at 248° and analyzed for C₁₄H₁₇N₃O₂ (M⁺ 259). The yield was 75%.

The methylation, acetylation and benzylation of the *N*-amido group in tetrahydroharmine was achieved by preparing the activated complex of the amide through sodium and toluene followed by reactions with acetic anhydride benzoyl chloride and a mixture of formic acid-formaldehyde respectively. The acetyl, benzoyl and dimethyl derivatives were melted at 242°, 135-6° and 203° respectively.

N-Amido tetrahydroharmine when sulphonated with glacial acetic acid-sulphuric acid mixture, afforded the corresponding sulphonic acid derivative as shining light grey prismatic plates which did not melt up to 360° and analyzed for C₁₄H₁₆N₃O₂SO₃H. The position of the sulphonic acid group in the aromatic ring could not be ascertained through proton NMR spectrum as the product was not soluble in common deuterated solvents.

According to recent studies carried out by Siddiqui and Bina [2] on cyano derivatives of the conessine series

of alkaloids and some simpler bases, the cyanamides obtained through Von Braun cyanogen bromide reaction yielded amido, diamine and guanidine derivatives on careful hydrolysis, reduction, and treatment with ammonia respectively. In so far, however, as it was further noted in related studies that bases with ring nitrogen fail to yield these products, it is significant that in the case of tetrahydroharmine, which is a B carboline base with a ring nitrogen the amido derivative has been obtained in good yield from the cyano base.

EXPERIMENTAL

Cyanotetrahydroharmine. Tetrahydroharmine (5 g) was dissolved in 50 ml chloroform with the help of little methanol and to it was added an ethereal solution of 2.9 g BrCN at 5° with constant stirring. Under continued stirring 100 ml ether was then added on to the reaction mixture and a small quantity of crystalline hydrobromide of the unconverted tetrahydroharmine which settled down was filtered off. The filtrate was exhaustively shaken out with 20% acetic acid to eliminate the last traces of unreacted tetrahydroharmine. The ethereal layer was washed, dried (Na₂SO₄) and concentrated under reduced pressure. On cooling in ice-chest beautiful pale yellow prismatic plates of cyano tetrahydroharmine were obtained which melted at 280° (yield was 3.5 g, 70% of the theoretical). It analyzed for C₁₄H₁₅N₃O. (Found: C 68.5, H 6, N 17%; and M⁺ peak at 241. C₁₄H₁₅N₃O, requires: C 69.7%, H 5.8%, N 17.42% and mol. wt. 241). The IR spectrum in KBr showed C≡N stretching vibration at 2250 cm⁻¹, in addition to peaks for indolic -NH, -OCH₃ and benzene ring which are common to tetrahydroharmine.

N-Amido tetrahydroharmine. Cyano tetrahydroharmine (2 g) was taken up in 20 ml alcohol and 15 ml 10% NaOH was added on to it. On refluxing the solution for half-an-hour with the addition of 20 ml 30% hydrogen peroxide and cooling the reaction mixture colourless shining crystals separated out which were filtered, repeatedly washed with water. On recrystallization with methanol the product melted at 248°. The yield of N-amido tetrahydroharmine thus obtained was 1.6 g (ca. 75% of theoretical yield). It analyzed for C₁₄H₁₇N₃O₂. (Found: C 64, H 6.4, N 16.216% and M⁺ peak at 259. Calcd for C₁₄H₁₇N₃O₂ C 64.8, H 6.56%, N 16.216%; and mol. wt. 259). The IR spectrum in KBr showed a doublet for amide NH₂ at 3500 and 3550 cm⁻¹, indolic -NH (3200 cm⁻¹), carbonyl stretching of amide (1690 cm⁻¹), NH₂ bending of amide group (1620 cm⁻¹) and other peaks at 1600 cm⁻¹, 1490 and 680 cm⁻¹ for C=C vibration of benzene ring. The proton NMR spectrum in deuterated dimethyl sulphide was

similar to that of tetrahydroharmine with an additional peak for the protons of the amide group at δ5.95 (2H singlet).

Acetylation of N-Amido tetrahydroharmine. N-Amido tetrahydroharmine (250 mg) was taken in 10 ml toluene, and refluxed for 24 hr with the addition of sodium metal. The turbid solution was heated for about 3 hr after the addition of 2 ml freshly distilled acetic anhydride and a few drops of dry pyridine. The reaction mixture was basified with a strong solution of ammonia and exhaustively extracted out with ethyl acetate. The residue left on removal of the solvent after washing and drying was taken up in hot acetone. On concentration and cooling the solution in ice-chest acetyl N-amido tetrahydroharmine was obtained as colourless crystalline needles, m.p. 241°. The molecular formula C₁₇H₁₉N₃O₃ was confirmed by mass spectrometry (M⁺ 301). The IR and proton NMR spectrum were similar to tetrahydroharmine with additional band at 1720 cm⁻¹ for N-acetyl carbonyl group and a 3H

singlet at δ3.4 for N-C(=O)-CH₃ group respectively.

Benzoylation of N-Amido tetrahydroharmine. N-Amido tetrahydroharmine (250 mg) in 10 ml of toluene was refluxed with 0.5 g pure sodium metal for 24 hr. To it was added 2 ml benzoyl chloride. The reaction mixture was heated at 70-80° for about an hour, basified with a strong solution of ammonia and exhaustively extracted out with ethyl acetate. The ethyl acetate layer was well-washed with water, dried and concentrated, when on cooling in ice-chest benzoyl N-amido tetrahydroharmine was obtained as prismatic rectangular plates, m.p. 135°. The molecular formula C₂₁H₂₁N₃O₃ was confirmed by mass spectrometry (M⁺ 363). The IR and NMR spectra were similar to that of tetrahydroharmine with additional band at 1700 cm⁻¹ for benzoyl carbonyl group and a 5H singlet at δ7.5 for phenyl group respectively.

Methylation of N-Amido tetrahydroharmine. N-amido tetrahydroharmine (0.25 g) was refluxed with 0.5 g pure sodium metal and 10 ml toluene for 24 hr. The resulting activated complex was extracted out with formic acid and 1.8 ml formaline solution was added to the formic acid-soluble fraction. The reaction mixture was refluxed for 24 hr, ammoniated and exhaustively extracted out with ethylacetate. The ethylacetate layer was well-washed and dried (Na₂SO₄) when on concentration dimethyl N-amido tetrahydroharmine was obtained as colourless rectangular plates, m.p. 238°. The molecular formula C₁₆H₂₁N₃O₂ was confirmed by mass spectrometry (M⁺ 287). The IR and NMR spectra were similar to N-amidotetrahydroharmine except for the absence of doublet at 3350 and 3500 cm⁻¹ in IR spectrum and the absence of singlet of amide -NH₂ group and the presence of singlet for two N-CH₃

groups at δ 2.24 in NMR spectrum.

Sulphonation of N-Amido tetrahydroharmine. N-amido tetrahydroharmine (0.25 g) was dissolved in 2 ml glacial acetic acid and 5 ml fuming sulphuric acid was added on to it at 0° . The reaction mixture was kept at this temperature for about 15 min then poured in crushed ice. The pH of the solution was brought to 5.5 by the addition of concentrated ammonia solution. On keeping the still warm solution in the cold, beautiful grey rectangular plates were obtained which did not melt up to 360° . It analyzed for $C_{14}H_{16}N_3O_2SO_3H$. (Found: C 49.49, H 5.2, N 12.5, S 9.5%. $C_{14}H_{16}N_3O_2SO_3H$ requires: C 49.56, H 5.014, N 12.389, S 9.439%, mol. wt. 339).

The IR spectrum in KBr showed S=O stretching

vibration at 1350 cm^{-1} in addition to other peaks for indolic -NH, OCH_3 , $\overset{''}{C}$ -NH and benzene ring which are common to N-amido tetrahydroharmine.

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