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## SOME EXTENSIONS OF VON BRAUN (BrCN) REACTION ON ORGANIC BASES: PART V

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In continuation of studies in the structure and activity relationship, a number of new derivatives of 8-amino-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline have been prepared through some extensions of von Braun BrCN reaction.

### INTRODUCTION

As a result of studies in the extensions of von Braun BrCN reaction, a number of new derivatives of various categories of alkaloidal and simpler bases have been reported earlier [1-6]. The present paper deals with the studies of a series of hitherto unreported derivatives obtained from 8-amino-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (8-aminotetrahydroharmine) [7] generally in high yields.

8-Amino-2-cyano-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (I) was obtained on reaction of 8-amino-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline with freshly prepared cyanogen bromide. Due to its extreme sensitivity to heat and light it was converted to its stable colourless hydrochloride on which various reactions described below were carried out. The $^1$HNMR spectrum of I recorded immediately after its liberation, showed a two-protons signal at δ 3.73 exchangeable with $D_2O$ for $-NH_2$ group and a one-proton quartet at δ 4.36 for $C_1$-–H.

I on reaction with $AC_2O$/pyridine and BzCl/NaOH yielded the acetyl (II) and benzoyl (III) derivatives respectively. The $^1$HNMR spectrum of II showed two one-proton broad signals at δ 10.00 and δ 8.03, attributable to amide NH and indolic NH while the aromatic protons were shifted towards lower field (δ 7.2, $C_5$–H; δ 6.8, $C_6$–H), due to the presence of $COCH_3$ group at $C_8$ amino nitrogen. The protons of acetyl group appeared as a sharp singlet at δ 2.26.

When treated with 1.2 moles of benzenesulphonyl chloride, I afforded the monobenzenesulphonamido derivative (IV), which on reaction with diazomethane gave the methyl derivative (VI) indicating the acidic character of the sulphonamido proton. The sulphonamido derivative also gave the corresponding acetyl derivative (VII) in theoretical yield. Furthermore, on treatment with excess of benzenesulphonyl chloride I afforded the dibenzenesulphonamido derivative V. All these observations collectively led to the location of the cyano group at pyrido nitrogen in I.

On the other hand, I on reaction with a further quantity of BrCN (1.2 moles) furnished 8-(N-cyano) amino-2-cyano-7-methoxyl-1-methyl-1,2,3,4-tetrahydro-β-carboline (VIII).

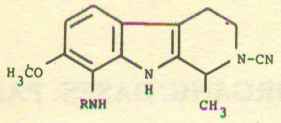
Attempts at the hydrolysis of I in acidic as well as basic conditions to obtain the corresponding amido derivative proved ineffective. However, 8-acetamido-2-cyano-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (II) on hydrolysis with $H_2O_2$/NaOH yielded the amido derivative IX, the IR spectrum of which showed peaks for amido function while the –CN band was not observed. The $^1$HNMR spectrum of IX showed a two-protons broad singlet at δ 6.1 and a one-proton quartet at δ 5.33 due to $NCONH_2$ and the $C_1$–H respectively.

It was noted in the previous studies (loc. cit) that the cyanamides in which the nitrogen atom occurs in a ring system resist reduction to diamines. In the present studies, however, it has been possible to obtain diamine (X) on reduction of I with Zn/HCl, although in low yield.

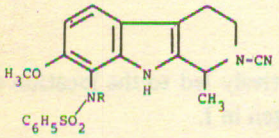
### EXPERIMENTAL

Melting points were recorded in glass capillary tubes and are uncorrected. IR and UV spectra were measured on IRA-1 Diffraction Grating Infrared Spectrophotometer and Shimadzu UV-VIS Recording Spectrophotometer UV-240 respectively. Proton NMR spectra were determined on JEOL PMX-60 and Bruker WP 100 SY instrument with TMS as internal reference. Mass spectra were recorded on MAT-112 and Varian MAT-312 Mass Spectrometer. The purity of the samples was checked on tlc (silica gel).

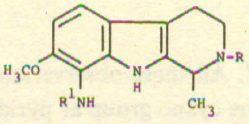
*8-Amino-2-cyano-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (I).* A solution of 8-aminotetrahydroharmine [7] (1 g) in ether-methanol (9:1) was treated with



I. R = H
II. R = $-COCH_3$
III. R = $-COC_6H_5$
IV. R = $-SO_2C_6H_5$
VIII. R = $-CN$



V. R = $-SO_2C_6H_5$
VI. R = $-CH_3$
VII. R = $-COCH_3$



IX. R = $-CONH_2$, $R^1$ = $-COCH_3$
X. R = $-CH_2-NH_2$, $R^1$ = H

an ethereal solution of freshly prepared cyanogen bromide (0.5 g) for about 10 min. in cold under stirring. The reaction mixture was then extracted out with 30% aqueous hydrochloric acid (10 ml x 3). The acidic solution was kept in cold overnight after adding sodium chloride till slight turbidity. The hydrochloride of I separated out as colourless crystallizate, which formed bunches of fine needles from methanol melting at 320° (decomp.). An additional quantity of the hydrochloride was obtained on working up the filtrate (yield 75%). It is soluble in water, methanol, and ethanol, and analysed for $C_{14}H_{16}N_4O$. HCl.

(Found C, 57.51; H, 5.84; N, 19.15; Cl, 12.00%;
Calcd. C, 57.53; H, 5.87; N, 19.18; Cl, 11.97%.

The base came out as colorless fine needles on treating the aqueous solution of the hydrochloride with ammonia, m.p. 110°C (decomp.). It is soluble in methanol, chloroform, and ethyl acetate, sparingly soluble in ether and insoluble in petroleum ether.

IR (KBr) $\nu_{max}$:3400 (indolic NH), 3300, 3280 ($-NH_2$ stretching), 2200 ($-C\equiv N$) and 1620 $cm^{-1}$ (aromatic C=C).

UV (MeOH) $\lambda_{max}$:225,273 and 293 nm $\lambda_{min}$:248 and 284 nm.

Mass: $M^+$ = 256.13241 (Calcd. for $C_{14}H_{16}N_4O$ = 256.13239). Other diagnostic peaks at m/e 241, 226, 201 and 187 (B.P.).

$^1$HNMR ($CDCl_3$) δ : 9.2 (1H, broad signal, indolic NH), 6.94 (1H, d, J = 8 cps, $C_5-H$), 6.75 (1H, d, J = 8 cps, $C_6-H$), 4.36 (1H, q, $C_1-H$), 3.86 (3H, s, $OCH_3$), 3.73 (2H, s, $NH_2$), 3.46 (2H, t, $N-CH_2$), 2.8 (2H, t, $4-CH_2$) and 1.46 (3H, d, J = 7, $C_1-CH_3$).

*8-Acetamido-2-cyano-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (II):* The acetate (II) obtained on treatment of I–HCl (0.5g) with acetic anhydride (2 ml) in pyridine (1 ml) at room temperature overnight and usual work up, formed colourless fine needles from methanol-benzene, mp. 170°C (yield theoretical). It is soluble in methanol, ethanol, acetone, and ethyl acetate, sparingly soluble in benzene and ether, insoluble in petroleum ether.

IR ($CHCl_3$) $\nu_{max}$: 3415 (indolic NH), 3300 ($CH_3CO-NH-$), 2220 ($-C\equiv N$), 1680 (amide C=O) and 1620 (aromatic C=C).

UV (MeOH) $\lambda_{max}$:206, 226, 276 and 294 nm $\lambda_{min}$: 212, 255 and 285 nm.

Mass: $M^+$ = 298.1428 (Calcd. for $C_{16}H_{18}N_4O_2$ = 298.1429). Other important peaks at m/e 283, 255, 241, 240, 187 and 43 (B.P.).

$^1$HNMR ($CDCl_3$) δ : 10.00 (1H, broad signal, indolic NH/amide NH), 8.03 (1H, broad signal, indolic NH/amide NH), 7.2 (1H, d, J = 8.5 cps, $C_5-H$), 6.80 (1H, d, J = 8.5 cps, $C_6-H$), 4.57 (1H, q, $C_1-H$), 3.91 (3H, s, $OCH_3$), 3.5 (2H, t, $N-CH_2$) 2.85 (2H, t, $4-CH_2$), 2.26 (3H, s, $COCH_3$) and 1.63 (3H, d, $C_1-CH_3$).

*8-Benzamido-2-cyano-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (III).* The benzoate (III) was obtained from I–HCl as colorless crystallizate on treatment with benzoyl chloride in 10% aqueous sodium hydroxide at room temperature for 30 min. and usual work up. It formed colourless bunches of needles from methanol-benzene (1:1), m.p. 182-84°, (yield 78%). It is soluble in ethanol, methanol, acetone, and ethyl acetate, sparingly soluble in benzene and ether, insoluble in petroleum ether.

IR($CHCl_3$) $\nu_{max}$:3400 (indolic NH), 3320 ($C_6H_5CO-NH$), 2200 ($-C\equiv N$), 1660 (amido C=O) and 1625 $cm^{-1}$ (aromatic C=C).

UV (MeOH) $\lambda_{max}$:204, 220, 272 and 296 nm, $\lambda_{min}$: 211, 258 and 283 nm.

Mass: $M^+$ = 360.1587 (Calcd. for $C_{21}H_{20}N_4O_2$ = 360.1586). Other diagnostic peaks at m/e 345, 225, 201, 105 (B.P.) and 77.

*8-Benzenesulphonamido-2-cyano-7-methoxy-1methyl-1,2,3,4-tetrahydro-β-carboline (IV).* A solution of I–HCl in pyridine (3 ml) was kept at room temperature with benzenesulphonyl chloride (0.5 ml) for I hour. The colourless crystallizate, obtained on usual work up, formed needles of IV on recrystallization from methanol, mp. 175-76°C. The residue, obtained from the mother liquor, afforded a second crop of the benzenesulphonamido derivative after

purification with ether and petroleum ether (yield 84%). It is soluble in methanol, ethanol, acetone and benzene, sparingly soluble in ether, insoluble in petroleum ether.

IR (KBr) $\nu_{max}$:3380 (indolic NH), 3280 ($C_6H_5SO_2$ –NH), 2200 (–C≡N), 1630 (aromatic C=C), 1340 and 1170 (O=S=O).

UV (MeOH) $\lambda_{max}$:204, 226, 273 and 297 nm, $\lambda_{min}$: 210, 256 and 284 nm. Mass: $M^+$ = 396.1256 (Calcd. for $C_{20}H_{20}N_4O_3S$ = 396.12558). Other diagnostic fragments at m/e 381, 255, 240, 201 (B.P.), 141 and 77.

*8-(N,N-Dibenzenesulphonyl) amino-2-cyano-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (V).* I–HCl (1 g) on reaction with excess of benzenesulphonyl chloride in aqueous sodium hydroxide (10% at room temperature for 30 min. and usual work up yielded the dibenzenesulphonyl derivative (V), which on crystallization from acetone-water (1:1) formed colorless rectangular plates melting at 212-14°C (yield 85%). It is soluble in acetone, methanol, ethanol and ethyl acetate, sparingly soluble in benzene and insoluble in petroleum ether.

IR ($CHCl_3$) $\nu_{max}$:3440 (indolic NH), 2220 (–C≡N), 1630 (aromatic C=C), 1360 and 1160 $cm^{-1}$ (O=S=O).

UV (MeOH) $\lambda_{max}$:204, 225, 267, 274 and 296 nm $\lambda_{min}$:210, 258, 270 and 280 nm.

Mass: $M^+$ = 536.1185 (Calcd. for $C_{26}H_{24}N_4O_5S_2$ = 536.1187). Other important peaks at m/e 521, 395, 380, 254, 239, 141 and 77 (B.P.)

*Methylation of IV to 8-(N-benzenesulphonyl-N-methyl) amino-2-cyano-7-methoxyl-1-methyl-1,2,3,4-tetrahydro-β-carboline* (VI). V (200 mg) was dissoved in anhydrous ether with the help of a little absolute methanol (9:1) and treated with an excess of ethereal solution of diazomethane in cold. The reaction mixture was kept at room temperature for about 1 hr. and freed of the solvent. The residue formed colourless small rods of VI from methanol-ether (1:2), m.p. 190-92°C (yield theoretical). It is soluble in ethyl acetate, benzene, chloroform, acetone, methanol and ether, sparingly soluble in petroleum ether.

IR (KBr) $\lambda_{max}$:3380 (indolic NH), 2210 (–C≡N), 1625 (aromatic C=C), 1350 and 1160 $cm^{-1}$ (O=S=O).

UV (MeOH) $\lambda_{max}$:204, 227, 273, and 296 nm, $\lambda_{min}$: 210, 257 and 283 nm.

Mass: $M^+$ = 410.1411 (Calcd. for $C_{21}H_{22}N_4O_3S$ = 410.1412). Other diagnostic peaks at m/e 395, 269 (B.P.), 254, 141 and 77.

*8-(N-Acetyl-N-benzenesulphonyl) amino-2-cyano-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (VII).* Reaction of V (200 mg) with acetic anhydride (1 ml) in pyridine (0.5 ml) at room temperature overnight and work-up in the usual manner gave the acetyl derivative (VII), which crystallized out from methanol in prismatic shining plates, m.p. 256°C (decomp.) (yield theoretical). It is soluble in acetone, methanol, ethyl acetate and chloroform, sparingly soluble in benzene and ether, insoluble in petroleum ether.

IR (KBr) $\nu_{max}$:3360 (indolic NH), 2200 (–C≡N), 1700 ($C_6H_5SO_2$ –N–C(=O)–$CH_3$), 1630 (aromatic C=C) 1365 and 1180 $cm^{-1}$ (O=S=O).

UV (MeOH) $\lambda_{max}$:205, 222, 273 and 308 nm. $\lambda_{min}$: 215, 260 and 290 nm.

Mass: $M^+$= 438.1361 (Calcd. for $C_{22}H_{22}N_4O_4S$ = 438.1361). Other important peaks at m/e 396, 381, 297, 282, 255, 201 (B.P.), 141, 77 and 43.

*8-(N-Cyano) amino-2-cyano-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (VIII).* An ethereal solution of freshly liberated base (I) (1 g) was treated with an ethereal solution of cyanogen bromide (0.5 g) with constant stirring and efficient cooling. The light pinkish crystalline precipitate which separated out immediately was washed thoroughly with warm 5% hydrochloric acid. The precipitate yielded VIII on recrystallization from methanol-benzene as colourless elongated needles, m.p. 280-82° (decomp.). It is soluble in methanol, acetone, sparingly soluble in ethyl acetate and chloroform, insoluble in ether and petroleum ether (yield 46%). The dicyanamide analyzed for $C_{15}H_{15}N_5O$ (Found: C, 64.04; H, 5.32; N, 24.95%; $M^+$ at m/e 281; required = C, 64.04; H, 5.34; N, 24.91% and mol. wt. 281). It showed –C≡N stretchings at 2230-2200 $cm^{-1}$.

The residue obtained on usual work up of the acidic washings obtained above, was identified as the monocyano derivative through comparison of TLC and spectral data with those of an authentic sample.

*Partial alkaline hydrolysis of II to 8-acetamido-2-amido-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (IX).* A methanolic solution of II (300 mg) was treated with 25% aqueous solution of NaOH (0.5 ml) and 30% hydrogen peroxide (1 ml) in cold under stirring. After about 3 hr. stirring at 40-45°, the reaction mixture was cooled, neutralized and concentrated under vacuum. It was exhaustively extracted out with ethyl acetate which on work up in the usual way, furnished the urea derivative as colourless crystallizate in nearly theoretical yield. On recrystallization from methanol-benzene (2:1) it formed prismatic rods, m.p. 245-46° (decomp.). It is soluble in methanol and acetone, sparingly soluble in ethyl acetate and chloroform, and insoluble in ether and petroleum ether.

IR (KBr) $\nu_{max}$:3440-3320 broad (indolic NH, primary amido $NH_2$ and secondary amido NH), 1670 strong broad

peak (amido C=O), 1600 strong sharp peak (amido NH bending).

UV (MeOH) $\lambda_{max}$:208,230,278 and 296 nm. $\lambda_{min}$: 214, 256 and 287 nm.

Mass: $M^+$ = 316.1532 (Calcd. for $C_{16}H_{20}N_4O_3$ = 316.1535). Other diagnostic peaks at m/e 301, 273, 272 and 258 (B.P.).

$^1$HNMR (DMSO-$d_6$) δ : 10.19 (1H, s, indolic NH/$CH_3$ CO-NH–), 9.36 (1H, s, in olic NH/$CH_3$CO–NH–), 7.33 (1H, d, J = 8 cps, $C_5$–H), 6.83 (1H, d, J = 8 cps, $C_6$–H), 6.1 (2H, s, –$CONH_2$), 5.33 (1H, q, $C_1$–H), 3.9 (3H, s, $OCH_3$), 2.13 (3H, s, $COCH_3$) and 1.48 (3H, d, J = 7 cps, $C_1$–$CH_3$).

*Reduction of I to 8-Amino-2-aminomethyl-7-methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline* (X). A solution of I–HCl (0.5 g) in 20% aqueous HCl was warmed on the water bath with Zn dust for 30 min. The unreacted Zn was filtered off and the residue obtained on usual work up of the filtrate was taken in ethyl acetate and repeatedly purified with ether and petroleum ether. The purified solution was freed of the solvent and the resulting residue extracted out with ether. The ethereal solution showed a single spot on TLC and afforded X on removal of the solvent as a colorless crystallizate, m.p. 266-68° (decomp.) (yield 30%). It is soluble in methanol, acetone, chloroform, and ethyl acetate, sparingly soluble in ether, insoluble in petroleum ether.

IR ($CHCl_3$) $\nu_{max}$:3400-3250 (Ar-$NH_2$, $CH_2$–$NH_2$, and indolic NH) and 1630, 1615, 1570 $cm^{-1}$.

Mass: $M^+$ = 260.1637 (Calcd. for $C_{14}H_{20}N_4O$ = 260.1636). Other diagnostic peaks at m/e 245, 230, 201 and 187 (B.P.).

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