Some Extensions of von Braun (BrCN) Reaction on Organic Bases

Salimuzzaman Siddiqui* and Bina S. Siddiqui

HEJ Postgraduate Institute of Chemistry, University of Karachi, Karachi-32, Pakistan

von Braun Cyanogen Bromide Reaction

Some extensions of von Braun cyanogen bromide reaction have been undertaken on conessine, isoconessine and two simpler bases, dimethyl α-naphthyl amine and diethyl amine. The monocyanamides of conessine and isoconessine yielded acid amides, amino-derivatives (diamines) and guanido derivatives on careful hydrolysis, reduction and treatment with ammonia, respectively. The simpler bases also formed the acid amides and diamines but failed to give the guanido derivatives under the conditions employed for conessine series. Diamines of all these bases yielded carbinol amines on reaction with nitrous acid.

The von Braun BrCN reaction has been of considerable value to studies in the correlation of structure and activity in the field of alkaloids with particular reference to the nature of various radicals introduced at the secondary basic nitrogen, resulting from the reaction. Primarily the reaction serves to convert tertiary into secondary amines on the following pattern, while it also brings about the breakdown of cyclic amines [1, 2].
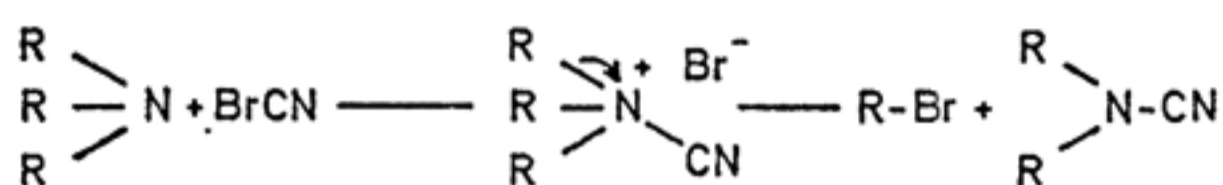

Studying the influence of the β–γ-unsaturated radicals introduced into the norbases of morphine and codeine obtained through the cyanogen bromide reaction, von Braun *et al.*, arrived at the conclusion that the status of unsaturation in that position vitally affects the physiological activity of the mother bases. Allyl-normorphine and allyl-nor-codein were thus found to have a reversal of their activity, functioning as stimulants instead of inhibitors of respiration [3, 4].

In the conessine series of alkaloids the cyanogen bromide reaction [5] was of great help in clarifying the relationship of the six subsidiary bases isolated by Siddiqui *et al.* from *Holarrhena antidysenterica* [6–8]. This was brought about through the hydrolysis of mono- and di-cyano derivatives of conessine which respectively furnished the mono- and di-norbases, isoconessimine and conimine, isolated from the bark and seeds of the plant. The methylation of these and other subsidiary bases to conessine with the help of formaldehyde and formic acid established the fact, that these alkaloids vary from each other in the number and position of the methyl groups attached to the two basic nitrogen atoms.

In so far as the constitutions of conessine series of bases have been fully established through comprehensive studies by various groups of workers [9–24] and as these bases are a potential source of physiologically significant derivatives, the present work has been undertaken to examine the feasibility of arriving at these derivatives through certain reactions of the cyanamides of the bases. As a result of these studies it has been possible to obtain from monocyanoconessine an acidamide introducing a urea moiety in the steroidal molecule through careful partial hydrolysis. On the other hand through reduction with zinc and hydrocholoric acid a diamine has been obtained, while treatment with ammonia furnished a guanidine derivative. Further, the diamine has yielded a carbinol amine through careful reaction with nitrous acid. All these derivatives have been obtained in fairly good yields (60–70%), and microanalytical data correspond to their molecular formulae. The spectral data of these derivatives are recorded below:

Conessine: R = CH₃
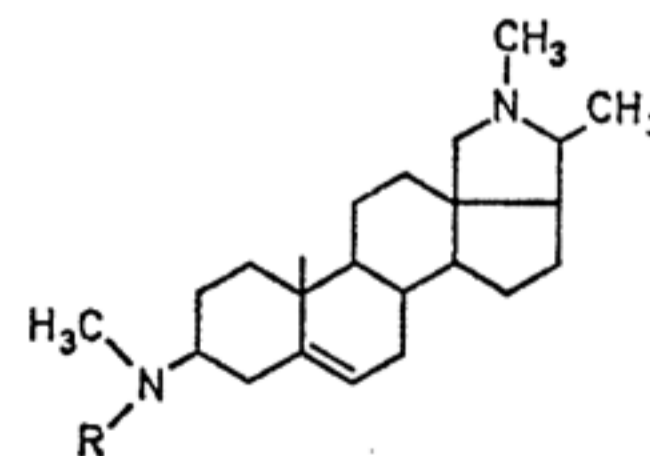
R		
–CH₂NH₂	N-Aminomethylisoconessimine	170 °C
–CH₂OH	N-Hydroxymethylisoconessimine	97 °C
–C(=O)–NH₂	N-Amidoisoconessimine	155 °C
–C(=N)–NH₂	N-Guanidoisoconessimine	145 °C

* Reprint requests to Prof. Dr. S. Siddiqui.

0340–5087/80/0800–1049/$ 01.00/0

Experimental

N-Amidoisoconessimine

$C_{24}H_{39}N_3O$

Found   C 74.73   H 10.09   N 11.05   O 4.23,
Calcd   C 74.8   H 10.12   N 10.90   O 4.18.

m.p. 155–156 °C; mass spectrum: M⁺ 385: other prominent fragments at m/e 370, 341, 314, 113, 71; IR ν_{max} (KBr): 3400, 3350, 1660, 1590 cm⁻¹; NMR (CDCl₃): δ 0.93 s (3 H, angular methyl protons), δ 1.06 d (3 H, 21-methyl protons), δ 2.22 s (3 H, ring N-methyl protons) δ 2.37 s (3 H, side chain N-methylprotons), δ 5.4 m (C₆–H), δ 6.73–6.86 m

$$\underset{(2\,H,\ -\overset{\displaystyle O}{\underset{\|}{C}}-NH_2).}{}$$

N-Aminomethylisoconessimine

$C_{24}H_{41}N_3$

Found   C 77.53   H 11.01   N 11.21   N–CH₃ 8.01,
Calcd   C 77.62   H 11.05   N 11.32   N–CH₃ 8.08.

m.p. 170–171 °C; mass spectrum: M⁺ 371, other prominent peaks at m/e 356, 341, 99, and 71; IR ν_{max} (KBr): 3350, 3400, 1620 cm⁻¹; NMR (CDCl₃): δ 0.93 s (3 H, angular methyl protons), δ 1.05 d (3 H, 21-methyl protons), δ 2.22 s (3 H, ring N–CH₃), δ 2.32 s (3 H, side-chain N–CH₃), δ 1.5 s (2 H, –NH₂), δ 5.34 m (1 H, C₆–H), and δ 2.9 s (2 H, N–CH₂–N–).

N-Hydroxymethylisoconessimine

$C_{24}H_{40}N_2O$

Found   C 77.33   H 10.25   N 7.47   OH 4.46,
Calcd   C 77.41   H 10.75   N 7.52   OH 4.32.

m.p. 97–98 °C; mass spectrum: M⁺, 372; other significant fragments at m/e 357, 354, 341, 100 and 71; IR ν_{max} (KBr): 3300–3400, 1055 cm⁻¹: NMR (CDCl₃): δ 0.93 s (3 H, angular methyl protons), δ 1.05 d (3 H, 21-methyl protons), δ 2.2 s (3 H, ring N–CH₃), δ 2.32 s (3 H, side-chain, N-methyl protons), δ 5.34 m (C₆–H), δ 4.15 s (2 H, N–C$\underline{\text{H}}_2$–OH).

N-Guanidoisoconessimine

$C_{24}H_{40}N_4$

Found   C 75.06   H 10.39   N 14.64,
Calcd   C 75.0   H 10.41   N 14.58.

m.p. 145–146 °C; mass spectrum M⁺, 384; other prominent fragments at m/e 369, 341, 112 and 71; IR ν_{max} (KBr): 3300, 3200, 1660, 1640 cm⁻¹:

NMR (CDCl₃): δ 3.8 s (2 H, $-\overset{\displaystyle NH}{\underset{\|}{C}}-NH_2$), δ 0.93 s (3 H, angular methyl protons), δ 1.05 d (3 H, 21-methyl protons), δ 2.2 s (3 H, ring N-methyl), δ 2.37 s (3 H, side chain N-methyl protons) and δ 5.36 m (1 H, C₆–H).

It may be noted as already pointed out by Siddiqui *et al.* that the monocyano derivative of conessine is formed at the amino group at position 3 and not at the ring nitrogen, as expected on the basis of von Braun's observations in regard to comparative N-stability of radicals attached to the tertiary amines.

An extension of these reactions to isoconessine furnished the corresponding derivatives as described below:
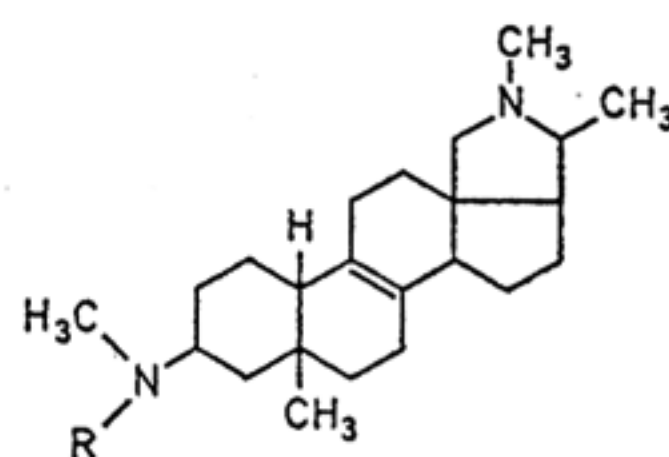
Isoconessine: R = -CH₃

R

–CH₂NH₂   N-Aminomethylisonorisoconessine

–CH₂OH   N-Hydroxymethylisonorisoconessine

$-\overset{\displaystyle O}{\underset{\|}{C}}-NH_2$ N-Amidoisonorisoconessine

$-\overset{\displaystyle HN}{\underset{\|}{C}}-NH_2$ N-Guanidoisonorisoconessine

N-Amino-methylisonorisoconessine

$C_{24}H_{41}N_3$

Found   C 77.58   H 11.15   N 11.17   N–CH₃ 8.11,
Calcd   C 77.62   H 11.05   N 11.32   N–CH₃ 8.08.

m.p. 278–279 °C; mass spectrum: M⁺, 371; other prominent peaks at m/e 356, 341, 99 and 71; IR ν_{max} (KBr): 3420, 3400, 1600 cm⁻¹; NMR (CDCl₃): δ 0.91 s (3 H, angular methyl protons), δ 1.01 d (3 H, 21-methyl protons), δ 2.2 s (3 H, ring N–CH₃ protons), δ 2.33 s (3 H, side chain N-methyl protons), δ 1.8 s (2 H, –NH₂), δ 3.01 s (N–CH₂–N).

N-Hydroxymethylisonorisoconessine

$C_{24}H_{40}N_2O$

Found   C 77.19   H 10.67   N 7.69   OH 4.23,
Calcd   C 77.41   H 10.75   N 7.52   OH 4.32.

m.p. 220–221 °C; mass spectrum: M⁺, 372; other prominent fragments at m/e 357, 354, 341, 100 and 71; IR ν_{max} (KBr): 3400–3300, 1060 cm⁻¹: NMR (CDCl₃): δ 4.1 s (2 H, N–C$\underline{\text{H}}_2$–OH), δ 0.91 s (3 H, angular methyl protons), δ 1.01 d (3 H, 21-methyl protons), δ 2.2 s (3 H, ring N-methyl protons), δ 2.33 s (3 H, side chain N-methyl protons).

N-Amidoisonorisoconessine

$C_{24}H_{39}N_3O$

Found   C 74.77   H 10.35   N 11.06   O 3.99,
Calcd   C 74.8   H 10.12   N 10.91   O 4.15.

m.p. 105–106 °C; mass spectrum M⁺, 385; other significant fragments at m/e 370, 341, 113 and 71; IR ν_{max} (KBr): 3380, 3400, 1660, 1595 cm⁻¹;

NMR (CDCl$_3$): δ 6.74–6.9 m ($-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{NH}_2$), δ 0.92 s (3 H, angular methyl protons), δ 1.01 d (3 H, 21-methyl protons), δ 2.2 s (3 H, ring N-methyl protons), δ 2.38 s (3 H, side chain N-methyl protons).

N-Guanidoisonorisoconessine

$C_{24}H_{40}N_4$

Found C 75.18 H 10.56 N 14.49,
Calcd C 75.0   H 10.41 N 14.58.

m.p. 95–96 °C; mass spectrum: M$^+$, 384; other prominent peaks at m/e 369, 341, 112 and 71; IR ν_{max} (KBr): 3300–3220, 1660, 1630 cm^{-1};

NMR (CDCl$_3$): δ 3.82 s (2 H, $-\overset{\overset{\text{NH}}{\|}}{\text{C}}-\text{NH}_2$), δ 0.91 s (3 H, angular methyl protons), δ 1.01 d (3 H, 21-methyl protons), δ 2.2 s (ring N-methyl protons), and δ 2.37 s (side chain N-methyl protons).

With the object of ascertaining their applicability on simpler bases, these reactions were carried out with the cyanamides of diethylamine and N,N-dimethyl-α-naphthylamine. In both these cases it was possible to obtaine the urea derivative and the diamine through partial hydrolysis and reduction respectively, but under the experimental conditions followed with conessine it was not possible to get the guanidine derivative from either of these bases. The microanalysis of these derivative (carried out through crystalline salts or derivatives in case of liquid bases) correspond to the molecular formulae noted below:
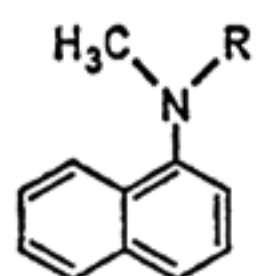
N, N-Dimethyl-α-naphthylamine, R = -CH$_3$

R
$-CH_2NH_2$ N-Aminomethyl, N-methyl-α-naphthylamine
$-CH_2OH$ N-Hydroxymethyl, N-methyl-α-naphthylamine
$-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{NH}_2$ N-Amido, N-methyl-α-naphthylamine

N-Aminomethyl, N-methyl-α-naphthylamine hydrochloride

$C_{12}H_{14}N_2 \cdot 2\, HCl$

Found C 55.71 H 6.09 N 11.05 Cl 27.53,
Calcd C 55.59 H 6.17 N 10.89 Cl 27.41.

m.p. 178–179 °C; spectral studies were carried out with the liquid base; mass spectrum: M$^+$, 186, other prominent fragments at m/e 171, 156, 127; IR ν_{max}: 3390, 3420, 1570 cm^{-1}; NMR (CDCl$_3$): δ 1.3 s (2 H, $-NH_2$), δ 2.95 s (3 H, N–CH$_3$), δ 3.41 s (2 H, $-N-CH_2-N$), δ 7.1–8.03 m (arom. protons).

N-Hydroxymethyl, N-methyl-α-naphthylamine

$C_{12}H_{13}NO$

Found C 76.89 H 7.05 N 7.61 O 8.45,
Calcd C 77.0   H 6.95 N 7.48 O 8.57.

m.p. 102–103 °C, mass spectrum M$^+$, 187, other prominent peaks at m/e 172, 169, 156, 141, 127; IR ν_{max} (KBr): 3300–3420, 1060 cm^{-1}; NMR (CDCl$_3$): δ 2.88 s (3 H, N–CH$_3$), δ 7.2–7.9 m (arom. protons), δ 4.18 s (2 H, N–CH$_2$–OH).

N-Amido, N-methyl-α-naphthylamine

Mass spectrum: M$^+$, 200, other prominent fragments at m/e 185, 156, 127, 44; IR ν_{max} (KBr): 3360, 3400, 1665, 1600 cm^{-1}; NMR (CDCl$_3$): δ 2.9 s (3 H, N–CH$_3$), δ 6.85 m (2 H, $-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{NH}_2$), δ 7.0–8.0 m (aromat. protons).

$\underset{\text{Diethyl amine: R = -H.}}{C_2H_5-\overset{\overset{\text{R}}{|}}{N}-C_2H_5}$

R
$-CH_2NH_2$ N-Aminomethyldiethylamine
$-CH_2OH$ N-Hydroxymethyldiethylamine
$-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{NH}_2$ N-Amidodiethylamine

N-Aminomethyldiethylamine hydrochloride

$C_5H_{14}N_2 \cdot 2\, HCl$

Found C 34.35 H 9.23 N 15.98 Cl 40.63,
Calcd C 34.29 H 9.14 N 16.0   Cl 40.57.

m.p. 310–311 °C. Spectral data as carried out through the liquid base–mass spectrum: M$^+$, 102; other important fragments at m/e 87, 72 and 30; IR ν_{max} 3450, 3500, 1600 cm^{-1}; NMR (CDCl$_3$): δ 1.3 t (6 H, 2-CH$_3$), δ 3.15 s (2 H, $-N-CH_2-N$), δ 1.5 s ($-NH_2$), δ 2.78 q (4 H, 2-N–CH$_2$–CH$_3$).

N-Hydroxymethyldiethylamine – acetate

$C_7H_{15}NO_2$

Found C 57.84 H 10.39 N 9.57 O 22.2,
Calcd C 57.93 H 10.34 N 9.65 O 22.08.

m.p. 130–131 °C; spectral data as carried out through liquid base; mass spectrum: M$^+$, 103 other prominent peaks at m/e 88, 85, 72, 31; IR ν_{max}: 3400–3250, 1050 cm^{-1}; NMR (CDCl$_3$): δ 1.28 t (6 H, 2-CH$_3$), δ 2.79 q (4 H, 2-N–CH$_2$–), δ 4.03 s (2 H, N–CH$_2$–OH).

N-Amidodiethylamine

$C_5H_{12}N_2O$

Found C 52.09 H 10.53 N 24.32 O 13.86,
Calcd C 51.72 H 10.34 N 24.13 O 13.73.

m.p. 70–71 °C; mass spectrum: M^+, 116; other fragments at m/e 101, 72, 44; IR ν_{max}: 3500, 3430, 1650, 1580 cm^{-1}; NMR (CDCl$_3$): δ 1.3 t (6 H, 2-CH$_3$), δ 2.8 q (4H, 2-N–CH$_2$–), δ 6.8 m (–$\overset{\overset{\textstyle O}{\|}}{C}$–NH$_2$).

Further work in this direction is being pursued with various categories of alkaloidal and simpler bases.

[1] J. v. Braun and Schwarz, Chem. Ber. 35, 1279 (1902).

[2] J. v. Braun, Chem. Ber. 49, 2624 (1916).

[3] J. v. Braun, Chem. Ber. 47, 2312 (1914).

[4] J. v. Braun, R. Kuhn, and S. Siddiqui, Chem. Ber. 59, 1081 (1926).

[5] S. Siddiqui and R. H. Siddiqui, J. Indian Chem. Soc. 11, 787 (1934).

[6] S. Siddiqui and P. P. Pillay, J. Indian Chem. Soc. 9, 553 (1932).

[7] S. Siddiqui, J. Indian Chem. Soc. 11, 283 (1934).

[8] S. Siddiqui, Proc. Indian Acad. Sci. 3 A, 249 (1936).

[9] Warnecke, Ber. (1886) 19, 60; Arch. Pharm. (1886) (3), 26, 248, 281.

[10] F. Ulrici, Arch. Pharm. 57, 256 (1918).

[11] G. Giemsa and J. Halberkann, Arch. Pharm. 256, 201 (1918).

[12] Kanga Iyyer and Simensen, J. Chem. Soc. 1926, 2123.

[13] E. Spaeth and O. Hromatka, Ber. 63 B, 126 (1930).

[14] S. Siddiqui, Proc. Indian Acad. 2 A, 426 (1935).

[15] S. Siddiqui and S. K. Vasishta, J. Sci. Ind. Res. (India) 3, 559 (1945).

[16] S. Siddiqui, R. H. Siddiqui, and S. K. Sharma, Proc. Indian Acad. Sci. 4 A, 283 (1936).

[17] S. Siddiqui and V. N. Sharma, Proc. Indian, Acad. Sci. 6 A, 191 (1937).

[18] R. D. Haworth, J. Mckenna, and N. Singh, J. Chem. Soc. 1949, 831.

[19] R. D. Haworth, J. Mckenna, and N. Singh, Nature (London) 22, 162 (1948).

[20] A. Bertho, Liebigs Ann. Chem. 1, 569 (1950).

[21] F. Sorm, L. Labler, and V. Cerny, Chem. Listy 48, 1058 (1954).

[22] R. D. Haworth, Chem. Soc. (London) Spec. Publ. No. 3, 1 (1955).

[23] B. Bailey, R. D. Haworth, and J. Mckenna, J. Chem. Soc. 1954, 967.

[24] H. Faver and B. Marinier, Can. J. Chem. 36, 429 (1958).