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

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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 carbinal 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].

[Diagram]

Hydrolysis
Decarboxylation

The relationship 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-norcodein 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-norbasises, isooncessin and comine, isolated from the bark and seeds of the plant. The methylolation 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 monocyanooconessine an acidamide introducing a urea moiety in the steroidal molecule through careful partial hydrolysis. On the other hand through reduction with zinc and hydrochloric acid a diamine has been obtained, while treatment with ammonia furnished a guanidine derivative. Further, the diamine has yielded a carbinal 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:

1. \(-\text{CH}_2\text{NH}_2\) N-Aminomethylisoconessimine 170 °C
2. \(-\text{CH}_2\text{OH}\) N-Hydroxymethylisoconessimine 97 °C
3. O
4. \(-\text{C}-\text{NH}_2\) N-Amidoisoconessimine 155 °C
5. N
6. \(-\text{C}-\text{NH}_2\) N-Guanidoisoconessimine 145 °C
Experimental

**N-Amidoisoconessimine**

\( C_{24}H_{39}N_3O \)

Found C 74.73 H 10.09 N 11.05 O 4.25,
Caled 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, 113, 71; IR \( \nu_{\text{max}} \) (KBr): 3400, 3350, 1660, 1590 cm\(^{-1}\); NMR (CDCl\(_3\)): \( \delta \) 0.93 s (3H, angular methyl protons), \( \delta \) 1.06 d (3H, 21-methyl protons), \( \delta \) 2.22 s (3H, ring N-methyl protons) \( \delta \) 3.27 s (3H, side chain N-methyl protons), \( \delta \) 5.4 m (C\(_6\)-H), \( \delta \) 6.73–6.86 m (O)

\( (2H, -\text{C}=\text{N}-\text{H}) \).

\( \text{N-Amino-methylisoconessimine} \)

\( C_{24}H_{41}N_3 \)

Found C 77.53 H 11.01 N 11.21 N-CH\(_3\) 8.01,
Caled C 77.62 H 11.05 N 11.32 N-CH\(_3\) 8.08.

m.p. 170–171 °C; mass spectrum: M+ 371, other prominent peaks at m/e 356, 341, 99, and 71; IR \( \nu_{\text{max}} \) (KBr): 3350, 3400, 1620 cm\(^{-1}\); NMR (CDCl\(_3\)): \( \delta \) 0.93 s (3H, angular methyl protons), \( \delta \) 1.05 d (3H, 21-methyl protons), \( \delta \) 2.22 s (3H, ring N-CH\(_3\)), \( \delta \) 2.32 s (3H, side-chain N-CH\(_3\)), \( \delta \) 5.34 m (IH, C\(_6\)-H), and \( \delta \) 2.9 s (2H, N-CH\(_2\)-N–).

\( \text{N-Hydroxymethylisoconessimine} \)

\( C_{24}H_{40}N_2O \)

Found C 77.33 H 10.25 N 7.47 OH 4.46,
Caled 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 \( \nu_{\text{max}} \) (KBr): 3300–3400, 1055 cm\(^{-1}\); NMR (CDCl\(_3\)): \( \delta \) 4.1 s (2H, N-CH\(_2\)-OH), \( \delta \) 0.91 s (3H, angular methyl protons), \( \delta \) 1.01 d (3H, 21-methyl protons), \( \delta \) 2.2 s (3H, ring N-CH\(_3\)), \( \delta \) 2.33 s (3H, side-chain N-methyl protons), \( \delta \) 1.8 s (2H, -NH\(_2\)), \( \delta \) 3.01 s (N-CH\(_2\)-N).

\( \text{N-Guanidoisoconessimine} \)

\( C_{24}H_{40}N_4 \)

Found C 75.06 H 10.39 N 14.64,
Caled 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 \( \nu_{\text{max}} \) (KBr): 3300, 3200, 1660, 1640 cm\(^{-1}\):

NMR (CDCl\(_3\)): \( \delta \) 3.8 s (2H, -C=NH\(_2\)), \( \delta \) 0.93 s (3H, angular methyl protons), \( \delta \) 1.05 d (3H, 21-methyl protons), \( \delta \) 2.2 s (3H, ring N-methyl), \( \delta \) 2.87 s (3H, side chain N-methyl protons) and \( \delta \) 5.36 m (1H, C\(_6\)-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 isononessine furnished the corresponding derivatives as described below:
NMR (CDCl₃): δ 6.74–6.9 m (–C-NH₂), δ 0.92 s (3H, angular methyl protons), δ 1.01 d (3H, 21-methyl protons), δ 2.2 s (3H, ring N-methyl protons), δ 2.38 s (3H, side chain N-methyl protons).

N-Methyl-α-naphthylamine

Found C 75.18 H 10.56 N 14.49
Caled C 75.00 H 10.41 N 14.58

N-N-Dimethyl-α-naphthylamine

R = -CH₃

R

-CH₂NH₂ N-Aminomethyl, N-methyl-α-naphthylamine

-CH₂OH N-Hydroxymethyl, N-methyl-α-naphthylamine

O

-Cl NH₂ N-Amido, N-methyl-α-naphthylamine

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

C₁₂H₁₄N₂ · 2 HCl

Found C 55.71 H 6.09 N 11.05 Cl 27.53
Caled 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 85, 87, 127; IR vₑₑₐ₉ (KBr): 3390, 3420, 1570 cm⁻¹; NMR (CDCl₃): δ 1.5 s (2H, –NH₂), δ 2.95 s (3H, N-CH₃), δ 3.41 s (2H, –NH₂ –N), δ 7.1–8.03 m (aromatic protons).

N-Hydroxymethyl, N-methyl-α-naphthylamine

C₁₂H₁₉NO

Found C 76.89 H 7.05 N 7.61 O 8.45
Caled 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 vₑₑₐ₉ (KBr): 3300–3420, 1060 cm⁻¹; NMR (CDCl₃): δ 2.88 s (3H, N-CH₃), δ 7.2–7.9 m (aromatic protons), δ 4.18 s (2H, N-CH₂-OH).

N-Amido, N-methyl-α-naphthylamine

Mass spectrum: M⁺, 200, other prominent fragments at m/e 185, 168, 127, 44; IR vₑₑₐ₉ (KBr): 3360, 3400, 1660, 1600 cm⁻¹; NMR (CDCl₃): δ 2.9 s (3H, N-CH₃), δ 6.85 m (2H, –C-NH₂), δ 7.0–8.0 m (aromatic protons).

R

C₂H₅-N-C₂H₅

Diethylamine: R = -H.

R

-CH₂NH₂ N-Aminomethyl diethylamine

-CH₂OH N-Hydroxymethyl diethylamine

O

| N-CH₂-OH | N-Amido diethylamine

N-Aminomethyl diethylamine hydrochloride

C₇H₁₅NO₂ · 2 HCl

Found C 57.84 H 10.39 N 9.57 Cl 40.63
Caled C 57.93 H 10.34 N 9.65 Cl 40.57

m.p. 130–131 °C. Spectral data as carried out through liquid base; mass spectrum: M⁺, 102; other important fragments at m/e 87, 72 and 30; IR vₑₑₐ₉ (KBr): 3450, 3500, 1600 cm⁻¹; NMR (CDCl₃): δ 1.3 t (6H, 2-CH₃), δ 3.15 s (2H, –NH₂ –N), δ 1.5 s (–NH₂), δ 2.78 q (4H, 2-N-CH₂–CH₂–CH₃).

N-Hydroxymethyl diethylamine – acetate

C₇H₁₅NO₂

Found C 57.84 H 10.39 N 9.57 Cl 40.63
Caled C 57.93 H 10.34 N 9.65 Cl 40.57

m.p. 130–131 °C; spectral data as carried out through liquid base; mass spectrum: M⁺, 103 other prominent peaks at m/e 85, 87, 72, 31; IR vₑₑₐ₉ (KBr): 3400–3250, 1050 cm⁻¹; NMR (CDCl₃): δ 1.28 t (6H, 2-CH₃), δ 2.79 q (4H, 2-N-CH₂–CH₂–CH₃), δ 4.03 s (2H, N-CH₂–OH).

N-Amido diethylamine

C₅H₁₄N₂O

Found C 52.09 H 10.53 N 24.32 O 13.86
Caled 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 νmax: 3500, 3430, 1650, 1580 cm⁻¹; NMR (CDCl₃): δ 1.3 t (6H, 2-CH₃), δ 2.8 q (4H, 2-N-CH₂), δ 6.8 m (–C=NH₂).

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

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