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N-ALLYL AND N-ALKYL DERIVATIVES OF MONO-NOR-BASES OF CONESSINE SERIES

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N-allyl and *N*-alkyl derivatives of mono-nor-bases of conessine series, isoconessimine and isonor-isoconessine, have been prepared and characterized through physical and chemical data.

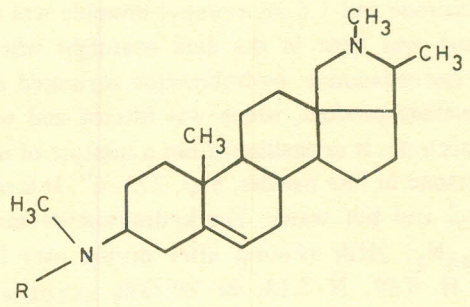
INTRODUCTION

In the course of studies in the correlation of structure and activity in the morphine series of alkaloids, it was observed by Von Braun *et al.* [1], that the degree of unsaturation in β-γ - position of the radicals attached to the basic nitrogen atom vitally affects the physiological activity of the mother bases. Allyl normorphine and allylnorcodeine were thus found to undergo a reversal of their activity, functioning as stimulants instead of inhibitors of respiration.

It was further noted by them that this reversal is linked with the decrease of the *N*–stability of these radicals in so far as the saturation of the double bond in case of allyl nor-codeine restored its original inhibitory action on respiration.

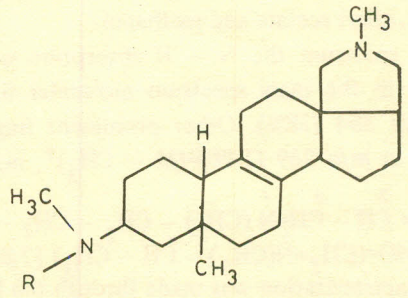
It was observed in the conessine series, that while conessine on Hofmann degradation, yields apoconessine in small yields with the elimination of one molecule of methanol and trimethylamine,[2,3] the quarternary bases iso-and neo-conessine gave back the tertiary bases in theoretical yields with the elimination of two molecules of methanol[4,5]. On the other hand, while the monocyanamides of the isomeric bases gave the dicyano derivatives within an hour on reaction with cyanogen bromide, the mono cyanamide of conessine afforded the dicyano derivative on keeping the reaction mixture for nearly a whole week.

In view of these findings, it was considered of interest to prepare the allyl and alkyl derivatives of the mono–nor–bases of the conessine series and study their influence on physiological activity, with particular reference to any variations in their inhibitory action on respiration. As a result of studies in this direction the following products have been obtained; and their pharmacological study is awaited.



Isoconessimine, R= – H

N-Propyl isoconessimine R = $-CH_2-CH_2-CH_3$
N-butyl isoconessimine R = $-CH_2-(CH_2)_2-CH_3$
N-pentyl isoconessimine R = $-CH_2-(CH_2)_3-CH_3$
N-allyl isoconessimine R = $-CH_2-CH=CH_2$



Iso–nor–isoconessine, R = – H

N-propyl-iso-nor-isoconessine, R= $-CH_2-CH_2-CH_3$
N-butyl-iso-nor-isoconessine, R= $-CH_2-(CH_2)_2-CH_3$
N-pentyl-iso-nor-isoconessine, R= $-CH_2-(CH_2)_3-CH_3$
N-allyl-iso-nor-isoconessine, R= $-CH_2-CH=CH_2$

All these products have been characterized through physical and chemical data provided in the experimental.

EXPERIMENTAL

Melting points were recorded in capillary tubes and are uncorrected. IR spectra were measured with a SP 200

G spectrophotometer in $CHCl_3$. Proton NMR spectra were determined in deutrated chloroform on JEOL PMX 60 instrument operating at 60 MHz with TMS as internal reference. Mass spectra were obtained on V.G. Micromass 12 at 70 electron volt and 3.5 KV accelerating voltage. The purity of the samples was checked on TLC (silica gel).

The mono–nor–bases isoconessimine and iso–nor–isoconessine were prepared through the reaction of conessine and isoconessine with BrCN and subsequent hydrolysis of the cyanamides, following the procedures recorded by Siddiqui *et al.* [4,6] . Both the nor-bases were obtained in theoretical yields.

N–*Propyl isoconessimine.* Isoconessimine (1 g) was dissolved in acetone and 1.5 ml *n*-propyl bromide was added. The mixture was kept in the dark overnight when the *N*–propyl isoconessimine hydrobromide separated out as white crystalline product, which was filtered and washed well with acetone. It crystallised from a mixture of methanol and acetone in fine needles, m.p. 275–6°. It is soluble in methanol and hot water. The hydrobromide analysed for $C_{26}H_{44}N_2$. 2HBr (Found after drying over P_2O_5: C 57.25, H 8.49, N 5.13, Br 29.73%; calculated for $C_{26}H_{44}N_2$. 2HBr: C 57.14, H 8.42, N 5.12, Br 29.3%). The free base (0.9 g; yield 80.3%) which was liberated with ammonia, crystallised from moist ethyl acetate as elongated needles, m.p. 70 – 1°, and analysed for $C_{26}H_{44}N_2$ (Found after drying over P_2O_5: C 81.32, H 11.53, N 7.15%. $C_{26}H_{44}N_2$ requires: C 81.25, H 11.45, N 7.29%). It is soluble in ether, ethyl acetate and methanol.

In the IR spectrum the N – H absorption was not observed while in the mass spectrum molecular ion was observed at *m/e* 384 (28%). Other prominent fragments were observed at *m/e* 369 (14%)=$(M - CH_3)^+$, *m/e* 112 (100%)=$(\overset{1}{C}H_2 = \overset{2}{C}H - \overset{3}{C}H = \overset{+}{N}(CH_3) - CH_2 - CH_2 - CH_3)$ and *m/e* 71 (74%)=$(CH_2 = \overset{+}{N}(CH_3) - CH - CH_3)$ [7,8] .

Further characterization was made through the following salts:

Hydrochloride was obtained as white amorphous powder on addition of ethereal hydrochloric acid to an ethereal solution of the base. On crystallization from methanol it came out as fine shining needles, m.p. 302 – 3°. It is soluble in ethanol, methanol and hot water.

Chloroplatinate was obtained on adding 3% aqueous solution of chloroplatinic acid to an acidic solution of the base, as silky yellow needles, m.p. 320 – 1°. It is insoluble in methanol and sparingly soluble in hot water.

Pricate, m.p. 130 – 1°, came out in the form of shining yellow needles on adding aqueous picric acid to an aqueous solution of the hydrobromide and cooling overnight. It is soluble in methanol, less so in ethyl acetate and insoluble in water.

N-*Butylisoconessimine.* It was prepared by adding *n*–butyl bromide (1 ml) to acetone solution of the base (1 g) and working up the reaction mixture in the same way as described above. The *N*–butyl isoconessimine hydrobromide crystallised as bunches of needles, m.p. 340 – 1°, and analysed for $C_{27}H_{46}N_2$. 2HBr (Found after drying over P_2O_5: C 58.01, H 8.91, N 5.05, Br 28.96. Calculated for $C_{27}H_{46}N_2$. 2HBr: C 57.85, H 8.57, N 5.0, Br 28. 57%). It is soluble in methanol and insoluble in water. The free base (yield 92%) was liberated from ammonia and crystallised from moist ethyl acetate as colourless rectangular plates m.p. 320°. It analysed for $C_{27}H_{46}N_2$ (Found after drying over P_2O_5: C 81.51, H 11.67, N 6.99. $C_{27}H_{46}N_2$ requires: C 81.4, H 11.55, N 7.03%).

The IR spectrum showed absence of NH group and the mass spectrum exhibited molecular ion at *m/e* 398 (27%). Other significant fragments were noted at *m/e* 383 (34%) = $(M - CH_3)^+$, *m/e* 126 (100%) = $(\overset{1}{C}H_2 = \overset{2}{C}H - \overset{3}{C}H = \overset{+}{N}(CH_3) - (CH_2)_3 - CH_3)$ and *m/e* 71 (71.50%) = $(CH_2 = \overset{+}{N}(CH_3) - \underset{20}{C}H - CH_3)$ [7,8] .

The following salts of *n*-butyl derivative were prepared in the same way as described above.

– Hydrochloride, m.p. 270 – 1° (decomp.)
– Chloroplatinate, m.p. 350°.
– Picrate, m.p. 156.

The hydrochloride and the picrate are soluble in methanol and sparingly so in hot water, while the chloroplatinate is insoluble in methanol and water.

N–*Pentylisoconessimine.* It was prepared by adding *n*-pentyl bromide (1 ml) to isoconessimine (1g) following the procedure noted above. The *N*-pentyl isoconessimine hydrobromide was obtained as fine needles on crystallization from methanol melting at 210 – 1° and analysed for $C_{28}H_{48}N_2$. 2HBr (Found after drying over P_2O_5: C 58.51, H 8.76, N 4.91, Br 28.03%. Required for $C_{28}H_{48}N_2$. 2HBr: C 58.53, H 8.71, N 4.87, Br 27.87%). It is soluble in methanol and sparingly in hot water. The free base (0.92 g. yield 76.6%) which was liberated from ammonia, crystallised from ethyl acetate as rectangular plates, m.p. 300 – 1°. It analysed for $C_{28}H_{48}N_2$ (Found after drying over P_2O_5: C 81.57, H 11.73, N 7.01%. Calculated for $C_{28}H_{48}N_2$: C 81.55, H 11.65, N 6.79%). The IR spectrum showed absence of N – H band and the mass spectrum showed molecular ion at *m/e* 412 (23.5%) in addition to other important peaks at *m/e* 397 (18%) = $(M - CH_3)^+$,

m/e 140 (100%) = $(\overset{1}{CH_2} = \overset{2}{CH} - \overset{3}{CH}=\overset{+}{N}(CH_3) - (CH_2)_4 - CH_3)$ and *m/e* 71 (78.9%) = $(CH_2 = \overset{+}{N}(CH_3) - \underset{20}{\dot{C}H} - CH_3)$ [7,8].

– Hydrochloride, m.p. > 320°
– Chloroplatinate, m.p. 308 – 9°.
– Picrate, m.p. 150 – 1°.

The hydrochloride and picrate are soluble in methanol and insoluble in water while the chloroplatinate is insoluble in methanol and sparingly soluble in hot water.

N-*Allylisoconessimine.* By following the above procedure the *N-allylisoconessimine* hydrobromide was obtained as white amorphous powder which formed shining needles from methanol melting at 284 – 5°. It analysed for $C_{26}H_{42}N_2$. 2HBr (Found after drying over P_2O_5: C 57.61, H 8.19, N 5.17, Br 29.23%. $C_{26}H_{42}N_2$. 2HBr requires: C 57.35, H 8.08, N 5.14, Br 29.49%). It is soluble in methanol and readily so in water. The free base (yield 90%) crystallised from moist ethyl acetate in the form of shining rectangular plates melting at 84 – 5°. It analysed for $C_{26}H_{42}N_2$ (Found after drying over P_2O_5: C 82.02, H 11.03, N 7.31%. Calculated for $C_{26}H_{42}N_2$: C 81.67, H 10.99, N 7.32%). The IR spectrum did not show any N – H absorption and the mass spectrum exhibited molecular ion at *m/e* 382 (17%) and other peaks at *m/e* 367 (14%)= $(M - CH_3)^+$, *m/e* 110 (100%) = $(\overset{1}{CH_2}=\overset{2}{CH} - \overset{3}{CH}=\overset{+}{N}(CH_3) - \dot{C}H_2 - CH=CH_2)$ and *m/e* 71 (74%)=$(CH_2=\overset{+}{N}(CH_3) - \underset{20}{\dot{C}H} - CH_3)$ [7,8].

The H^1 – NMR spectrum showed a three protons singlet at δ 0.93 (19 – angular methyl group), a three – protons doublet at δ 1.05 (21 methyl group), two three – protons singlets at δ 2.22 and δ 2.32 (ring and side – chain *N*-methyl groups respectively) a one – proton multiplet at δ 5.38 (C_6 – H) a two – protons doublet at δ 3.6 (– N – CH_2) a one – proton multiplet at δ 5.9 (– $CH=CH_2$) and a two – protons multiplet at δ 5.43 (– $CH=CH_2$).

– Chloroplatinate, m.p. 295 – 6°.
– Hydroiodide, m.p. 274 – 5°.
– Hydrochloride, m.p. 310 – 11°.
– Picrate, m.p. 164 – 5°.

The hydroiodide, hydrochloride and picrate are soluble in hot methanol, ethanol and sparingly in hot water.

The alkyl and allyl derivatives of isonor-isoconessine were prepared by the same procedure which has been described for those of isoconessimine. These, derivatives however, failed to crystallize and their analyses were carried out through their crystalline hydrobromides.

N-*Propylisonorisoconessine.* *N*-Propyl isonorisoconessine hydrobromide formed fine needles from methanol, m.p. 280 – 1°, and analysed for $C_{26}H_{44}N_2$. 2HBr (Found after drying over P_2O_5: C 57.23, H 8.50, N 5.09, Br 29.21%. Calculated for $C_{26}H_{44}N_2$. 2HBr: C 57.14, H 8.42, N 5.12, Br 29.3%). It is soluble in methanol and insoluble in water. The free base (yield 85%) showed the absence of N – H absorption in the IR spectrum and showed the molecular ion at *m/e* 384 (21.3%) in the mass spectrum; other important fragments were observed at *m/e* 369 (29.5%)=$(M - CH_3)^+$, *m/e* 112 (100%) = $(\overset{1}{CH_2}=\overset{2}{CH}-\overset{3}{CH}=\overset{+}{N}(CH_3) - CH_2 - CH_2 - CH_3)$, *m/e* 138 (47%)=$(CH_3 - CH_2 - CH_2 - \overset{+}{N}(\overset{3}{CH_3})=\overset{4}{CH} - \overset{5}{CH}= \overset{6}{CH}- \overset{7}{CH}=CH_2)$ and *m/e* 71 (73.3%) = $(CH_2=\overset{+}{N}(CH_3) - \underset{20}{\dot{C}H} - CH_3)$ [7,8].

The following salts of the *N*-propyl derivative were prepared employing the procedure described for conessine series.

– Hydroiodide, m.p. 262 – 3°, prismatic rods from water. It is soluble in hot water and hot ethanol and methanol.

– Pricrate, m.p. 151 – 2°, shining yellow needles from moist methanol. It is soluble in methanol, ethanol and insoluble in water.

– Chloroplatinate, m.p. 276 – 8°. It is insoluble in water, methanol, ethanol and acetone.

N-Butylisonorisoconessine. *N*-Butylisonorisoconessine hydrobromide formed rectangular plates from methanol – benzene, m.p. 293 – 4°, and analysed for $C_{27}H_{46}N_2$. 2HBr (Found after drying over P_2O_5: C 57.81, H 8.60, N 5.1, Br 28.59%. $C_{27}H_{46}N_2$. 2HBr requires: C 57.85, H 8.57, N 5.0, Br 28.57%). It is readily soluble in methanol, ethanol and water and insoluble in less polar solvents. The free base (yield 95%) showed absence of N – H absorption in the IR spectrum. In the mass spectrum prominent peaks were observed at *m/e* 398 (21.5%)=M^+, 383 (15.9%)= $(M - CH_3)^+$, *m/e* 126 (100%)=$(\overset{1}{CH_2}=\overset{2}{CH} - \overset{3}{CH} = \overset{+}{N}(CH_3) - (CH_2)_3 - CH_3)$, *m/e* 152 (51%) =$(CH_3 - (CH_2)_3 - \overset{+}{N}(\overset{3}{CH_3})=\overset{4}{CH} - \overset{5}{CH}=\overset{6}{CH} - \overset{7}{CH}=CH_2)$ and *m/e* 71 (74.5%)= $(CH_2 =\overset{+}{N}(CH_3) - \underset{20}{\dot{C}H} - CH_3)$ [7,8].

– Hydroiodide, m.p. 279 – 80°, prismatic rods from

methanol – benzene (1:1). It is readily soluble in ethanol, methanol and sparingly in water.

– Picrate, m.p. 178 – 80°, shining yellow spikes of needles from methanol – water. It is sparingly soluble in water and readily soluble in ethanol and methanol.

– Chloroplatinate, m.p. 280 – 1°, (decomp). It is insoluble in methanol, ethanol and sparingly soluble in hot water.

N-*Pentylisonorisoconessine.* *N*-Pentylisonorisoconessine hydrobromide formed white fine needles from methanol – water, m.p. 270 – 2°, and analysed for $C_{28}H_{48}N_2$. 2HBr (Found after drying over P_2O_5: C 58.56, H 8.69, N 4.84, Br 27.91%. Required for $C_{28}H_{48}N_2$. 2HBr: C 58.53, H 8.71, N 4.87, Br 27.87%). It is insoluble in water and readily soluble in methanol and ethanol. The free *N*-pentyl base (yield 97%) showed absence of N – H absorption in the IR spectrum. In the mass spectrum important fragments were noted at *m/e* 412 (19.5%) M^+, *m/e* 397 (27.3%)= $(M\text{-}CH_3)^+$, *m/e* 140 (100%)=$(\overset{1}{C}H_2=\overset{2}{C}H - \overset{3}{C}H=\overset{+}{N}(CH_3) - (CH_2)_4 - CH_3)$, *m/e* 166 (53%) = $(CH_3 - (CH_2)_4 - \overset{+}{N}(CH_3)= \overset{3}{C}H - \overset{4}{C}H=\overset{5}{C}H - \overset{6}{C}H=\overset{7}{C}H_2)$ and *m/e* 71 (79%)= $(CH_2=\overset{+}{N}(CH_3) - \underset{20}{\overset{\bullet}{C}}H - CH_3)$ [7,8].

– Picrate, m.p. 132 – 3°, yellowish orange needles from methanol. It is sparingly soluble in ether, ethyl acetate, soluble in methanol, ethanol and insoluble in water.

– Chloroplatinate, m.p. 268 – 9°, failed to crystallise. It is insoluble in methanol, ethanol and water.

N-*Allylisonorisoconessine.* *N*-Allylisonorisoconessine hydrobromide crystallized from methanol – benzene in colourless rectangular plates, m.p. 296 – 7° (decomp.) and analysed for $C_{26}H_{42}N_2$. 2HBr (Found after drying over P_2O_5: C 57.39, H 7.98, N 5.17, Br 29.45. Calculated for $C_{26}H_{42}N_2$. 2HBr: C 57.35, H 8.08 N 5.14 Br 29.41%). It is readily soluble in water and methanol. The free base (yield 90%) showed absence of N – H absorption in the IR spectrum. In the mass spectrum the molecular ion was observed at *m/e* 382 (15.9%) and other important fragments at *m/e* 367 (24%) = $(M - CH_3)^+$, *m/e* 110 (100%)= $(CH_2=CH - \overset{+}{C}H=N - (CH_3)=CH_2 - CH=CH_2)$, *m/e* 71 (78%)=$(CH_2=\overset{+}{N}(CH_3) - \underset{20}{\overset{\bullet}{C}}H - CH_3)$, and *m/e* 136 (33%)= $(CH_2=CH - CH_2 - N(CH_3)=CH - \overset{4}{C}H=\overset{5}{C}H - \overset{6}{C}H=\overset{7}{C}H_2)$ [7,8].

The H^1 NMR spectrum showed a three – protons singlet at δ 0.91 (19–angular methyl), a three – protons doublet at δ 1.1 (21–methyl), two three protons singlets at δ 2.22 (ring *N*-methyl) and at δ 2.33 (side – chain *N*-methyl), a two-protons doublet at δ 3.29 ($N\text{–}CH_2$–), a one – proton multiplet at δ 5.91 (–CH=C–) and a two – protons multiplet at δ 5.41 ($–C=CH_2$).

– Picrate m.p. 78 – 9°, needles from methanol. It is soluble in methanol and hot water, sparingly in ether and insoluble in petroleum ether.

– Chloroplatinate, m.p. 266 – 7°. It is insoluble in water, methanol, ethanol and acetone.

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REFERENCES

1. J.V. Braun, R. Kuhn, S. Siddiqui, Chem. Ber., **59B**, 1081 (1926).
2. D.D. Kanga, P.R. Ayyer, and J.L. Simonsen, J. Chem. Soc., 2123 (1926).
3. E. Spaeth, and O. Hromatka, Chem. Ber., **63B**, 126 (1930).
4. S. Siddiqui, R.H. Siddiqui, and S.K. Sharma, Proc. Indian Acad. Sci., **4A**, 283 (1936).
5. S.K. Vasishta, D.Sc Thesis, Banaras Hindu University India. (1940).
6. S. Siddiqui, and R.H. Siddiqui, J. Indian Chem. Soc., **11**, 787 (1934).
7. W. Vetter P. Longevialle, F. Khuong-Huu Laine, Q. Khuong-Huu, and R. Goutarel, Bull. Soc. Chim. France, 1324, (1963).
8. L. Dolejs, V. Hanus, V. Cerny, and F. Sorm Coll. Czech, Chem. Comm., **28**, 1584 (1963).