# THE CONDENSATION OF HISTAMINE WITH CARBONYL COMPOUNDS

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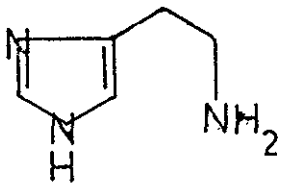
Substances of the spinaceamine type, 4,5,6,7-tetrahydroimidazo[5,6-c]pyridines can be obtained, by a biogenetic type synthesis, from histamine and carbonyl compounds in a buffer solution at pH 7.2 with an optimum yield.

Skin gland secretions from amphibians contain an amazing variety of mostly toxic compounds. Many of them are heterocyclic and a surprising fact is that almost every species of frogs possesses its own pattern of toxins. In the acetone extract of the skin of Leptodactylus pentadactylus labyrinthicus Erspamer, Vitali and Roseghini[1] have found, beside histamine (1), also spinaceamine (2a) and N-methylspinaceamine (2b). The biosynthesis of the latter may be explained by condensation of histamine (1) with a $C_1$-unit.

Spinaceamine had been obtained formerly by Wellisch,[2] and by Fränkel and Zeimer.[3] It is known from publications of Kendall and Bishop,[4] and of Kamimura[5] that histamine and aldehydes can react under mild conditions to yield compounds of type 2.



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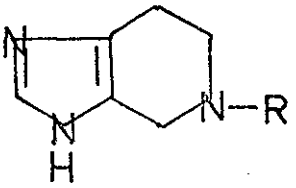


2 a R=H

2 b R=$CH_3$

In the course of extensive investigations on histamine-type compounds in toxins from frogs we found that spinaceamine possesses a remarkable antimicrobial activity.[6] Under these considerations we have reinvestigated the formation of spinaceamines with different substituents at C-7 by allowing histamine dihydrochloride to react with carbonyl compounds in aqueous solutions at 25° within a definite pH range.

No change took place on reacting histamine dihydrochloride and aldehydes or ketones unless a buffer was added at pH 6.7. However, the reaction took place on adding at least 1 equivalent of acetate buffer to the mixture. An optimum pH value was found at 7.2, based on systematic experiments, whereby the yield of spinaceamine rose to 90 %. Above and below this pH a remarkable decrease of the yield was observed; at a pH lower than 6.5 or above 8.5 histamine was recovered in practically quantitative yield when formaldehyde was used as a carbonyl compound.

More or less the same results were obtained in the reaction of histamine with acetaldehyde and benzaldehyde. In all of these cases a maximum yield has been obtained at pH 7.2; the yields, however, were lower than with formaldehyde.

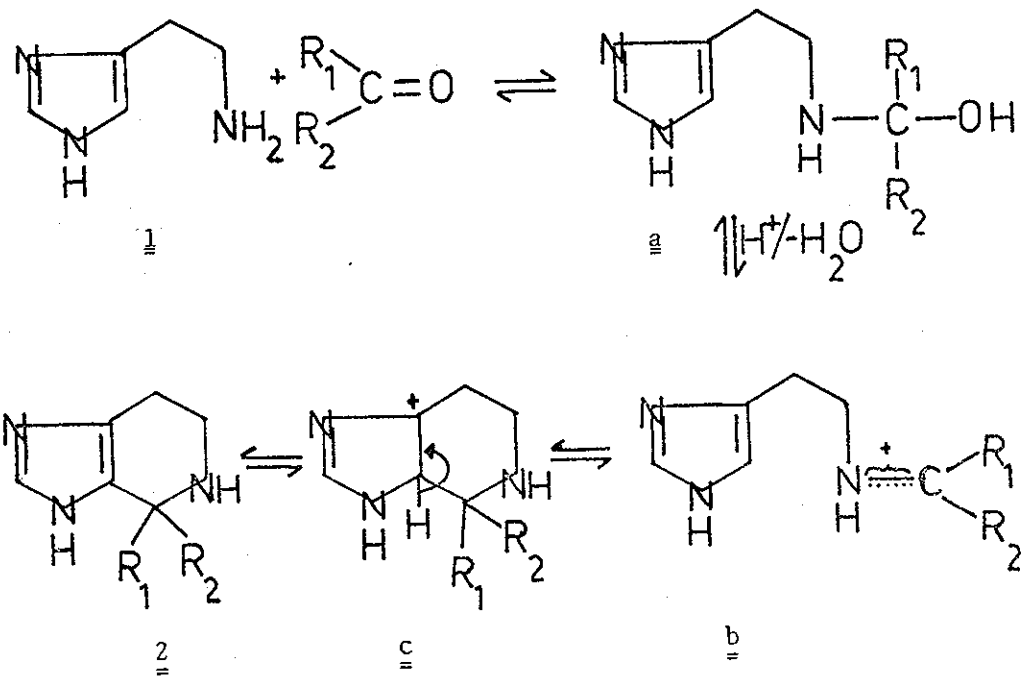
The yields were even lower with acetone while no reaction took place with ethyl methyl ketone as the carbonyl component.

Reaction products other than of the spinaceamine-type were not observed. This is expected, for carbon atom 7a (C-5 in histamine) is by far most favoured for an electrophilic substitution; the position is comparable to the site at which electrophilic attacks take place in pyrrole, and in addition it is a β-position of an enamine system comprising N-3, C-4, and C-5 of histamine.

From these facts we concluded that the reaction course depends on steric effects and that it is necessary to neutralize the hydrochloric acid quantitatively with a buffer. In acidic solution the reverse reaction is favoured whereas in alkaline solution aldol condensation or Cannizzaro reactions are faster than the formation of spinaceamines, so that only tars are formed.

Both 7-methylspinaceamine and 7-phenylspinaceamine possess a center of chirality, and thus are formed as racemates. Resolution of the antipodes was achieved in the case of 7-phenylspinaceamine which crystallizes well by using D-(-)-tartaric acid and L-(+)-tartaric acid, respectively, in isopropanol. From these salts the free bases were obtained. They showed an optical rotation of $[\alpha]_D^{20}$ = $-17.2^{\circ}$ and $+17.0^{\circ}$, respectively. These values decreased to $\pm 0^{\circ}$ in solution within 24 hours.

On addition of mineral acids racemization takes place immediately obviously via the stabilized carbonium ion b.



| | $R_1$ | $R_2$ |
|---|---|---|
| 2a: | H | H |
| 2c: | H | $CH_3$ |
| 2d: | H | $C_6H_5$ |
| 2e: | $CH_3$ | $CH_3$ |

## Experimental Part

Spinaceamine Dihydrochloride (4,5,6,7-Tetrahydroimidazo[5,6-c]-pyridine Dihydrochloride) (2a). Histamine Dihydrochloride (366 mg) (0.002 mole) in 60 ml of water was added to 100 ml of 2.0 M formaldehyde solution. The mixture was adjusted to pH 7.2 by M/5 acetate buffer. The solution was kept in a thermostat at 25° overnight. To the clear solution saturated, alcoholic picric acid solution was then added until a precipitate formed. After stirring for 1 hr at room temperature the precipitate was filtered and dried over $P_4O_{10}$. Picrate, m.p. 215 - 127°. This was converted into the hydrochloride by adding dilute hydrochloric acid to the picrate and extracting away the picric acid with nitrobenzene. After evaporation of the aqueous solution in vacuo the hydrochloride remained as colorless crystals. Recrystallization from absolute acetone yielded 344.6 mg (90 %) of spinaceamine hydrochloride, m.p. 267 - 269° (decomp).

$C_{16}H_{11}N_3Cl_2$ (195.8) calc. C 36.35, H 5.60, N 20.20
found C 36.13, H 5.73, N 20.07

The experimets with acetone and acetaldehyde were performed in the same way and their data have shown in Table 1.

7-Phenylspinaceamine (7-Phenyl-4,5,6,7-tetrahydroimidazo[5,6-c]pyridine). A solution of 366 mg (0.002 mole) of histamine dihydrochloride in 60 ml of water was prepared in a round bottom flask in a nitrogen atmosphere. Then 212 mg (0.002 mole) of freshly distilled benzaldehyde was added to the clear solution with vigorous stirring

and the pH was adjusted to 7.2 by a M/5 acetate buffer solution. The whole was kept stirring in a thermostat at 25° as long as a homogenous solution resulted, i.e. for 3 days. Then water was fully removed on a rotary evaporator and the residue extracted with 60 ml of hot ethanol. Upon filtration 90 mg (60 %) of a colorless product crystallized upon cooling, m.p. 196 - 198°.

$C_{11}H_{13}N_3$ (199.1) calc. C 72.34, H 6.58, N 21.09
found C 72.56, H 6.35, N 21.00

Resolution of 7-Phenylspinaceamine. (±)-Phenylspinaceamine 500 mg (0.0025 mole) in 150 ml of absolute n-propanol was added to a solution of 375 mg (0.0025 mole) of D-(-)-tartaric acid in 150 ml of n-propanol at 70°. On cooling, colorless crystals separated. Filtering and recrystallization from n-propanol gave 580 mg of tartrate, m.p. 122 - 124°. The salt was decomposed with 2 N NaOH and the free base extracted with ether. The extract was dried over sodium sulfate and evaporated in vacuo. Yield: 80 mg, m.p. 167 - 169°; $[\alpha]_D^{20} = -17.2°$.

In the same way, but using L-(+)-tartaric acid the other antipode had been obtained. Yield: 95 mg, m.p. 181 - 183°; $[\alpha]_D^{20} = +17.0°$.

Table 1 :

| 7,7-$R_1$.$R_2$-(4,5,6,7-tetrahydro-imidazo-5,6-c)-pyridine | M.p. | Mol. formula | Elemental Analysis C | H | N |
|---|---|---|---|---|---|
| $R_1$ = H $R_2$ = $CH_3$<br>7-Methyl-spinaceamine | Dipicrate: 220-222°C<br>Dihydrochloride: 289-291°C | $C_7H_{13}N_3Cl_2$ | -<br>calc.: 38.09<br>found: 37.69 | -<br>5.90<br>6.07 | -<br>19.09<br>19.10 |
| $R_1$ = H $R_2$ = Phenyl<br>7-Phenyl-spinaceamine | Free Base: 196-198°C | $C_{11}H_{13}N_3$ | calc.: 72.34<br>found: 72.56 | 6.58<br>6.35 | 21.09<br>21.00 |
| $R_1$ = $CH_3$ $R_2$ = $CH_3$<br>7,7-Dimethyl-spinaceamine | Dipicrate: 210-212°C | $C_{20}H_{19}N_9O_{14}$ | calc.: 39.41<br>found: 39.25 | 3.12<br>3.04 | 20.68<br>20.40 |

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