Formation of 3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1H-azepino [5,4,3-cd]indole in the reaction of serotonin with acetaldehyde in water in the presence of either L-amino acid, nicotine or fluoride

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FORMATION OF 3,4,5,6-TETRAHYDRO-7-HYDROXY-6-METHYL-1*H*-AZEPINO[5,4,3-*cd*]INDOLE IN THE REACTION OF SEROTONIN WITH ACETALDEHYDE IN WATER IN THE PRESENCE OF EITHER L-AMINO ACID, NICOTINE OR FLUORIDE[1]

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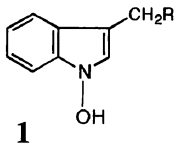
Abstract – Possible formation of a new compound, 3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1*H*-azepino[5,4,3-*cd*]indole (**4a**), in serotonergic neuron after drinking ethanol is chemically suggested by reacting serotonin with acetaldehyde in water in the presence of either L-amino acid, nicotine or fluoride.

In our "1-Hydroxyindole Hypotheses",[2] we have imagined the existence of 1-hydroxyindole derivatives such as 1-hydroxytryptamines (**1a**,**c**, Figure 1) and 1-hydroxytryptophans (**1b**,**d**) in serotonergic neurons, their conversion to serotonin congeners (**2a**—**d**), and their successive metabolism in the intraneuronal reaction either with aldehydes or with amines in the presence of reactive oxygen species (molecular oxygen, hydrogen peroxide, and superoxide) to cyclize to 1-substituted 6-hydroxytetrahydro-β-carbolines (**3**) and/or 6-substituted 3,4,5,6-tetrahydro-7-hydroxy-1*H*-azepino[5,4,3-*cd*]indoles (**4**). [2]

In reality, we have chemically succeeded in giving birth to thus far imaginary 1-hydroxyindole compounds (**1c** and **1d**),[2] and proved that they can be transformed to **2c** and **2d** under mild acidic conditions, effectively in 85% formic acid particularly. [2] Now, in this study, we wish to report that serotonin (**2a**) actually undergoes the expected cyclizations with acetaldehyde *in vitro* under model conditions of cytoplasm of serotonergic neurons.

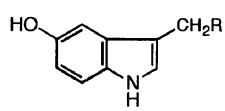
For the first time,[3] we have disclosed that serotonin hydrochloride (**2a**·HCl) produces a relatively unstable new compound, 3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1*H*-azepino[5,4,3-*cd*]indole (**4a**), and 1,2,3,4-tetrahydro-6-hydroxy-1-methyl-β-carboline[4] (**3a**), a Pictet-Spengler type condensation product, by the reaction either with Et_3N under molecular oxygen or with acetaldehyde.

Figure 1

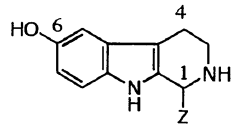


1

a) R = CH_2NH_2; b) R = $CH(NH_2)COOH$
c) R = CH_2NHR^1; d) R = $CH(NHR^1)COR^2$
R^1 = alkyl, acyl, etc. ; R^2 = OR^1, NHR^1, etc.

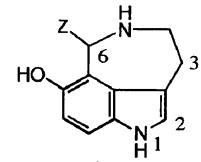


2



3

a) Z = Me; b) Z = C_6H_4(*p*-OMe),
c) Z = 2-Furyl, d) Z = Isobutyl



4

Table 1

2a·HCl —(MeCHO in Solvent; Air (Entries 1 and 3); Ar (Entries 2, 4—13))→ **3a** + **4a** + **2a**

Entry	Solvent	Additive (mol eq.)	MeCHO (mol eq.)	Reaction Conditions Temp. (°C)	Time (h)	Yield (%) of **3a**	**4a**	**2a**
1*[1]	MeOH	—	50	reflux	1	26	0	0
2	Pyridine	—	5	"	9	34	trace	37
3*[2]	MeOH	—	50	"	20	53	27	0
4	MeOH-H_2O (3:1)	K_2CO_3 (1)	5	"	20	11	12	52
5	Pyridine-H_2O (3:1)	K_2CO_3 (1)	"	"	3	0	30	4
6	MeOH	Imidazole (2)	"	"	4	3	7	28
7	MeOH-H_2O (3:1)	KF (2)	"	"	4	24	30	33
8	H_2O	L-Glutamic acid (2)	0.9	36.5	6	45*[3]	0	40
9	"	"	"	"	48	55*[3]	0	38
10	"	L-Histidine (2)	"	"	24	trace	12*[3]	63
11	"	L-Arginine (2)	"	"	15	5*[3]	31*[3]	38
12	"	Nicotine (2)	"	"	48	trace	17*[3]	42
13	"	KF (2)	"	"	120	22	5	53
14	"	—	"	"	72	55	0	39
15*[4]	"	—	"	"	24	6	23	46

*[1] The reaction was carried out at pH 4. *[2] The reaction was carried out at pH 5. *[3] The product was not optically active.
*[4] Starting material is serotonin itself (**2a**), not **2a·HCl**.

We have found that the product ratio of **3a** and **4a** depends on the acidity of the reaction medium. Acidic reaction conditions prefer the formation of **3a** to **4a**. Thus, the reaction of **2a**·HCl with acetaldehyde either at pH 4 in refluxing MeOH or in pyridine, **3a** was the only isolable product in 26 and 34% yields, respectively, together with tars (Table 1, Entries 1 and 2). On the other hand, under more basic reaction

conditions than pH 5.0, the formation of **4a** begins to be observed. Thus, the reaction of **2a**·HCl with acetaldehyde at pH 5 in refluxing MeOH, **3a** and **4a** were produced in 53 and 27% yields, respectively (Entry 3). The same reaction in the presence of K_2CO_3 in MeOH-H_2O afforded **3a** and **4a** in 11 and 12% yields, respectively, together with unreacted **2a** (52%, Entry 4). The reaction of **2a**·HCl with acetaldehyde in pyridine in the presence of K_2CO_3 produced **4a** as a sole product in 30% yield (Entry 5). In the presence of imidazole (2 mol eq.) in refluxing MeOH, acetaldehyde reacted with **2a**·HCl to give **3a**, **4a**, and recovered **2a** in 3, 7, and 28% yields, respectively (Entry 6). It is interesting to note that in the presence of KF (2 mol eq.) in refluxing MeOH-H_2O, **2a**·HCl afforded **3a**, **4a**, and recovered **2a** in 24, 30, and 33% yields, respectively (Entry 7).

As a model reaction within the cytoplasm of serotonergic neuron, **2a**·HCl was reacted with acetaldehyde (0.9 mol eq.) in H_2O at 36.5°C under argon atmosphere in the presence of various substance (2 mol eq.). As expected, L-glutamic acid catalyzed regioselective formation of **3a** and after 6 h it was obtained in 45% yield together with unreacted **2a** (40%, Entry 8). When the reaction time was extended to 48 h, the yield of **3a** increased up to 55% (Entry 9). In contrast, in the presence of L-histidine, the reaction of **2a**·HCl with acetaldehyde afforded **4a** regioselectively in 12% yield in addition to 63% yield of unreacted **2a** (Entry 10). Under similar reaction conditions except the presence of L-arginine, **4a** was produced in 31% yield after **2a**·HCl was reacted with acetaldehyde (Entry 11). (*S*)-(–)-Nicotine also catalyzed the condensation of **2a**·HCl with acetaldehyde resulting in the formation of **4a** in 17% yield after 48 h (Entry 12). In these reactions (Entries 8—12), products were not optically active. It should be noted that, in the presence of KF, **2a**·HCl reacted slowly but steadily with acetaldehyde to provide **3a** and **4a**, and after 120 h their yields reached to 22 and 5% yields, respectively (Entry 13). Without additive, **2a**·HCl afforded **3a** exclusively in 55% yield (Entry 14). The reaction of serotonin itself (**2a**) with acetaldehyde provided **3a** and **4a** in 6 and 23% yields, respectively (Entry 15). In addition, in MeOH **2a**·HCl was found to react with *p*-methoxybenzaldehyde, furfural, 3-methylbutanal to produce **3b—d** and/or **4b—d** and the results will be reported elsewhere.

Since ethanol is known to be metabolized to acetaldehyde in brain,[5] the above facts suggest that after drinking alcohol **4a** can be generated at either the L-histidine or L-arginine rich regions in the brain, while **3a** can be produced at the areas where L-glutamic acid rich proteins exist. Fluoride has been added to tap water to prevent teeth from decay in U.S.A., so if fluoride happens to get into serotonergic neurons, formations of **3a** and **4a** would also be predicted. Accepting alcohol and tobacco simultaneously is another important factor which facilitates the formation of **4a** by the catalysis of nicotine.

Considering that serotonin is known to play a role in feeding behavior, sleep, sexual function, and so on,[6] compound (**4a**) might be involved in numerous physiological and pathophysiological processes, particularly after ethanol drinking. Oxidative reaction[7] of both **4a** and serotonins[8] with reactive oxygen

species, analysis of the resultant products, their physiological actions, and interactions with various membrane receptors in the serotonergic neurons would be the urgent subjects to be solved.

In conclusion, we have discovered a possible formation of the new compound (**4a**) in brain and opened a door to a frontier of neurosciences. The compound (**4a**) would attract much attention of scientists in the brain research field as in the case of **3a**.[4,9]

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