

# PREPARATION AND PROPERTIES OF 3,4-DIHYDRO- $\beta$ -CARBOLINE

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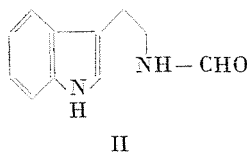
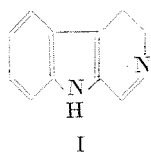
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As it was reported earlier [1], we succeeded in developing a convenient new synthesis for the preparation of substituted 2-oxo-octahydro-indolo(2,3-a)-quinolysines. These compounds may be considered as key substances in the synthesis of alkaloids of the indole skeleton that are of fundamental importance from a biological aspect.

On applying this method it is necessary to start from 3,4-dihydro- $\beta$ -carboline (I) as initial substance.



Base (I) has been first described by Japanese authors [2] as a tar-like substance obtained as the decomposition product of the evodiamine. It was identified by oxidizing it into  $\beta$ -carboline. The synthesis of I from N-formyl tryptamine (II) was attempted much later by SPÄTH and LEDERER. However, these authors obtained a yield of only 2% under the conditions of the conventional Bischler-Napieralsky synthesis [3]. In 1947 the problem was again investigated by SCHÖPF and STEUER [4] in connection with studies into the biogenesis of rutaecarpine and evodiamine. On modifying the earlier conditions of ring closure [3], a crude yield of 36% was obtained. Still, their method has the drawback of requiring excessive amounts (100 to 300-times as much) of solvent, and thus it is unsuitable for the preparation of large batches. The ring closure of acid amide II was carried out by ONDA and SASAMOTO [5] in pure phosphorus oxychloride. Quite recently, polyphosphoric acid was applied as a condensing agent by GUPTA and SPENSER [6] who obtained the desired end product (I) in a crude yield of 50%.

Base I is described by all the above mentioned authors as an amorphous substance with a prolonged melting point. Even after sublimation in a vacuum

of  $2 \cdot 10^{-3}$  (TORR [6]) a vitreous substance melting at a range from 90 to 130° was obtained. The analytical data of this substance were unfavourable. Attempts for preparing analytically pure product with the aid of chromatography similarly failed, in that only brown coloured polymers could be obtained.

After these tentative experiments, the present investigations were undertaken with the object already mentioned in the introduction.

On subjecting the conditions of the Bischler-Napieralsky ring closure of N-formyl tryptamine (II) to a thorough investigation, and on varying a number of parameters (such as condensing agent, solvent, temperature, way of preparation etc.), the conditions of optimum yield were established. In this way, crude base I was obtained in a yield of 85.5% in benzene using the procedure described in the experimental part with the aid of phosphorus oxychloride. For purposes of further syntheses, the crude product proved to be suitable with an efficiency nearly as high as that of the purified substance.

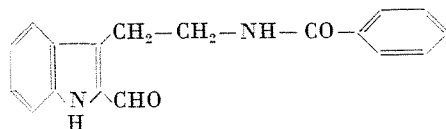
The base prepared in this way could be readily purified. On studying its properties it proved to crystallize in two allotropic modifications. It crystallized from benzene as well developed crystals of m. p. 84–85°, while on liberating the base from the salt by treatment with hot alkali, a substance with m. p. 173–177° was obtained. When the latter was recrystallized from hot benzene, similarly the modification with a lower m. p. was afforded. The analytical data and the chemical behaviour of both products were the same and corresponded with the expectations. Their different crystal structure was also proved by X-ray diagrams, while their infrared spectra were perfectly identical.

It is worth mentioning that the perchlorate of base I similarly showed two different melting points, depending on the conditions of crystallization. The substance recrystallized from ethanol melts at 216–217°, while the m. p. of the substance recrystallized from water is 177–180°. According to the X-ray investigations [7], the crystals belong to the same system, though their habitus is different. Their infrared spectra are, in turn, identical, and characterized, among others, by a band system appearing at a frequency of 1640 and 1570  $\text{cm}^{-1}$ , respectively. On recrystallizing the substance from heavy water, both bands were shifted by 20  $\text{cm}^{-1}$  to lower frequencies, indicating that the

above given absorption maxima are characteristic of the system  $-\overset{\parallel}{\text{N}}\text{H}-\overset{\parallel}{\text{C}}-\text{C}=\overset{|}{\text{N}}\text{H}(+)$ . In the deuterated compound the absorption of the valence vibration of the indole-ND bond can be observed at a range from 2300 to 2500  $\text{cm}^{-1}$ .

The reaction of 3,4-dihydro- $\beta$ -carboline with acylating agents (such as benzoyl chloride) is to be mentioned here as a chemical feature characteristic of its behaviour which differs from that of the related derivatives, e.g.  $\beta$ -car-

boline. While  $\beta$ -carboline and its derivatives undergo acylation on the nitrogen atom of the indole ring [8], under similar conditions the pyridine ring of compound I is cleaved and gives an oxo-compound III.



III

The synthesis of 3,4-dihydro- $\beta$ -carboline in fair yield, the preparation of an analytically pure product, and the elucidation of its properties made possible the use of this practical initial substance for purposes of further syntheses.

## Experimental

### 1. Tryptamine formate

On preparing tryptamine we started out from indole. *Gramine* was synthesized according to KÜHN and STEIN [9] with the modification that the aqueous solution of dimethylamine was prepared in the reaction mixture by treatment with alkali liberating dimethylamine from its salt. Accordingly, a dilute aqueous solution was applied that also contained an equivalent amount of sodium chloride. Our experiences proved that after the termination of the reaction it is advisable to add 5 *N* sodium hydroxide till no precipitate appears on the addition of further doses of alkali. The crude *gramine* was subjected to suction and thoroughly washed with water. The crude product with a m. p. was, very near to that given in literature, obtained in a practically quantitative yield.

$\beta$ -Indolyl acetonitrile was synthesized from *gramine* by the method of HENBEST et al. [10]. Omitting the vacuum distillation, the crude nitrile was directly used in the reduction process. The product was identified through its picrate prepared from the crude nitrile in 91% yield, with a m. p. identical with that given in literature [11].

The reduction of nitrile was carried out according to the prescription given in literature [11], the obtained tryptamine was identified as a formate and stored in this form.

The crude product was dissolved in a 20fold volume of ethyl acetate, treated with an equivalent amount of 94% formic acid, the precipitated crystals filtered under suction, and washed with ethyl acetate. In this way, the

salt with m. p. 167—168° was obtained in a yield of 90—97%. On repeated recrystallizations from ethanol, the m. p. did not rise over 168—169°.

Analysis:	$C_{11}H_{15}O_2N$
Calculated:	C 64.06 H 6.84 N 13.58%
Found:	C 63.96 H 6.60 N 13.75%

### 2. *N*-Formyl tryptamine (II)

Crude tryptamine formate was kept for 45 minutes at 180° in an oil bath. On cooling, crystals began slowly to appear, m. p. 75—76° (in literature [4] 76°). On withdrawing a small sample and dissolving it in a 5fold amount of ethyl acetate, we checked to see whether the reaction had already been completed. If a part of the substance did not dissolve (tryptamine formate) then the total amount of product must be dissolved, the solution filtered and the solvent removed by evaporation.

### 3. 3,4-Dihydro- $\beta$ -carboline (I)

22 g of *N*-formyl-tryptamine was boiled with 400 ml of anhydrous benzene until the major part of the substance dissolved. Then the mixture was cooled to some degrees below boiling point, and treated under shaking with 60 ml of dropwise added, freshly distilled phosphorus oxychloride. When the spontaneous boiling ceased, boiling was continued for 30 minutes in an oil bath preheated to 85—90°. Subsequently, the mixture was cooled to 40°, and the benzene as quickly as possible distilled off in vacuum. After the termination of the distillation, the contents of the flask were heated for another 10 minutes in vacuum on a hot water bath. The dark brown residue was vigorously shaken with 200 ml of 10% acetic acid. The originally almost hard mass adhering to the bottom of the flask became hot and is converted into a motile oil. This latter was thoroughly rubbed with further 300 ml of 10% acetic acid, made alkaline, shaken with  $4 \times 80$  ml of ethyl acetate, the residual solid substance subjected to suction, and thoroughly washed similarly with ethyl acetate. The combined solutions were dried on magnesium sulphate, cautiously evaporated to dryness in vacuum, and the residue kept for 3—4 minutes on a boiling water bath. Yield: 17.0 g (85.5%) of a golden yellow powder which could be used without any further purification for further syntheses [1]. This could be stored in sealed opaque containers.

0.30 g of the crude base was dissolved in 2 ml of 2 *N* acetic acid and treated with an equivalent amount of dropwise added dilute aqueous solution of perchloric acid. Immediately 0.4 g (84.3%) of a brownish red substance of

m. p. 215—217° was obtained (m. p. in literature [4]: 212—213°). On recrystallization from ethanol, yellow, well developed crystals, m. p. 216—217°.

$\lambda_{\text{max}}^{\text{EtOH}}$

$\nu_{\text{max}}^{\text{KBr}}$  1640  $\text{cm}^{-1}$  and 1570  $\text{cm}^{-1}$  ( $-\overline{\text{N}}\text{H}-\overset{\parallel}{\text{C}}-\overset{\uparrow}{\text{CH}}=\overset{\downarrow}{\text{N}}\text{H}$ )  
 $\oplus$

Analysis:  $\text{C}_{11}\text{H}_{10}\text{N}_2 \cdot \text{HClO}_4$  (270.68)  
 Calculated: C 48.81 H 4.09 N 10.35 Cl 13.09%  
 Found: C 48.96 H 4.15 N 10.10 Cl 12.52%

On recrystallizing the perchlorate from water, a yellow product with m. p. 177—180° was obtained. This had the same analytical composition and spectrum, though the habitus of crystals was different.

Melting points of other salts:

*Picrate*, 232—233° (from ether) (in literature [4]: 233°)

*Oxalate*, 210—211° (from ethanol)

*Benzoate*, 132—133° (from ethanol)

*Tartrate*, 201—202° (from ethanol)

*3,5-Dinitrobenzoate*, 225—226° (from ethanol)

*Styphnate*, 214—215° (from ethanol).

Base I was obtained from the perchlorate by treating the warm aqueous solution of the perchlorate with a 10% solution of sodium hydroxide under stirring. The liberated base had a creme tint, m. p. 173—177° (modification *A*). When the liberation process was carried out at lower temperature, then depending on the temperature of the solution, a substance with m. p. from 90 to 110° was obtained (a mixture of modifications *A* and *B*). On slowly heating this mixture it again solidified at 130° and melted at 173—177°. Essential differences exist in the behaviour of modifications *A* and *B* in respect to their solubility in benzene. While product *A* dissolves in benzene only on boiling, modification *B* is readily dissolved even in cold benzene. On allowing the solutions to stand, modification *B* precipitates from both solutions in the form of well developed white rhombic crystals with m. p. 84—85°.

$\lambda_{\text{max}}^{\text{EtOH}}$

$\nu_{\text{max}}^{\text{KBr}}$  340  $\text{cm}^{-1}$  (NH), 1630  $\text{cm}^{-1}$  and 1560  $\text{cm}^{-1}$  ( $-\overline{\text{N}}\text{H}-\overset{\parallel}{\text{C}}-\text{CH}=\overline{\text{N}}-$ )

Analysis:  $\text{C}_{11}\text{H}_{10}\text{N}_2$  (170.21)  
 Calculated: C 77.61 H 5.92 N 16.46%  
 Found: C 77.49 H 6.09 N 16.39%

Modification *A* (on drying over phosphorus pentoxide in vacuum at 60°) similarly gave the above adequate analytical data.

4. 2-Formyl-3( $\beta$ -benzoylamino-ethyl)-indole (III)

The solution of 0.8 g of base I in 4 ml of anhydrous pyridine was treated with 0.7 g of benzoyl chloride. On allowing the solution to stand overnight at room temperature, it was diluted with an excess of 5% soda solution. An oily product appeared which solidified after standing for a day. Yield: 1.35 g of crude product, m. p. 140–160°. On recrystallization from a mixture of benzene and petroleum ether, then from ethanol, 0.8 g of a white crystalline substance, m. p. 183°, was obtained which proved to be insoluble in acid.

Analysis:	$C_{18}H_{16}N_2O_2$ (292.33)
Calculated:	C 74.00 H 5.48 N 9.58%
Found:	C 74.11 H 5.59 N 9.40%

The infrared spectrum of the substance was in accordance with the presumed formula. The two secondary NH groups produced a band of about 3300  $cm^{-1}$ , while the conjugated formyl and the carbonyl of the acid amide bond created a merged band in the range 1660–1640  $cm^{-1}$ . The NH degenerated vibration appears at 1540  $cm^{-1}$ , the degenerated vibrations of the CH bonds perpendicular to the plane of the mono and disubstituted aromatic rings could be found at 753, 693 and 742  $cm^{-1}$ , respectively.

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## Summary

A method for the preparation of 3,4-dihydro- $\beta$ -carboline from N-formyl tryptamine in excellent yields was developed. The authors were the first in obtaining in two different allotropic modifications the mentioned base, in an analytically pure state.

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