## [CONTRIBUTION FROM THE NOVES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# The Synthesis of Derivatives of $\beta$ -Carboline. II. Syntheses from *dl*-Tryptophan and Aldehydes<sup>1</sup>

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Although compounds containing the  $\beta$ -carboline nucleus have been of great interest in connection with their occurrence in certain alkaloids, particularly in *Peganum harmala*<sup>6</sup> and *Alstonia constricta*,<sup>7</sup> relatively few synthetic members of this class have been prepared in quantity sufficient for physiological studies. Methods of synthesis have been devised,<sup>6</sup> but comparatively inaccessible raw materials such as *l*-tryptophan and tryptamine have been employed. Since *dl*-tryptophan is now readily available<sup>8</sup> it is of interest to consider its use in the preparation of derivatives of  $\beta$ -carboline.

The condensation of *l*-tryptophan with aldehydes, including formaldehyde, acetaldehyde and benzaldehyde,  $g^{-11}$  has been extended to the racemic amino acid. The aldehydes which have been employed in the condensation are acetaldehyde, benzaldehyde, phenylacetaldehyde, homoanisalde-



hyde, p-nitrobenzaldehyde, p-dimethylaminobenzaldehyde and hydratropic aldehyde (see Table

(1) For the preceding paper, see Snyder and Katz, THIS JOURNAL, 59, 3190 (1947).

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(6) "Thorpe's Dictionary of Applied Chemistry," Vol. VI, Longmans Green and Co., London, 1943, p. 186.

(7) Elderfield and Leonard, J. Org. Chem., 7, 556 (1942).

(8) Howe, Zambito, Snyder and Tishler, THIS JOURNAL, 67, 38 (1945).

(9) Jacobs and Craig, J. Biol. Chem., 113, 759 (1936).

(10) Harvey and Robson, J. Chem. Soc., 97 (1938).

(11) Harvey, Miller and Robson, ibid., 153 (1941).

I). The products (formula II) were obtained as mixtures of two racemic modifications in yields of 63-90%. The products from *dl*-tryptophan would not be expected to be identical with those from the natural amino acid. It is of interest that one of the isomers obtained from benzaldehyde and the racemic acid had a melting point (225-226°) near that reported (223-226°) for the product from the optically active amino acid,<sup>9</sup> whereas the products from acetaldehyde differed widely in melting points (247-248 and 258° for the racemic compounds, as compared to 290<sup>10</sup> or 297°<sup>9</sup> for the optically active substance).

The formation of isomers and the tendency to hydration often made the isolation of analytically pure specimens of the tetrahydro acids (II) extremely difficult, but did not interfere with the utilization of the substances in further syntheses. The condensation was unsuccessful when applied

to chloral hydrate, chloroacetal or formamide.

The methyl esters, obtained by esterification of the crude acids with methanol and dry hydrogen chloride, also formed hydrates, but in several instances analytically pure samples of the esters were obtained with much less difficulty than had been experienced with the acids. However, the separation of the diastereoisomeric forms proved no less difficult with the esters than with the acids. The products from acet-

aldehyde, phenylacetalde-

hyde and benzaldehyde were dehydrogenated to the fully aromatic compounds (IV,  $R = CH_3$ ,  $C_6H_6CH_2$  and  $C_6H_5$ , respectively). Various dehydrogenation procedures were tested on these and other tetrahydro esters, but no satisfactory general procedure was evolved. Methyl 1-methyl- $\beta$ -carboline-3-carboxylate (IV,  $R = CH_3$ ) and methyl 1-benzyl- $\beta$ -carboline-3-carboxylate (IV,  $R = C_6H_6CH_2$ ) were prepared by dehydrogenation with sulfur in refluxing xylene, and methyl 1-phenyl- $\beta$ -carboline-3-carboxylate was prepared by dehydrogenation with chloranil<sup>12,13</sup> in refluxing tetrachloroethane.

The aromatic acids corresponding to IV were prepared by saponification of the esters. Thionyl

(12) Clar and John, Ber., 63, 2967 (1930); *ibid.*, 64, 981 (1931).
(13) Arnold and Collins, THIS JOURNAL, 61, 1407 (1939); Arnold, Collins and Zenk, *ibid.*, 62, 983 (1940).

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	Acids								Methyl esters							
	Crude acids				Isomeric acids				Crude esters				Pure esters			
Qubatterine	м.р.,	Viold col		. м. р.,	Analyses, %		%	Round		Recry			Analyses, %			
in 1 position	(dec.)	07	venta	(100)	Calca.		C		м.р., ¥	x 1eid, sol-		м.р.,	Caled.		Found	
in i posición	(466.)	/0	Vent	(ucc.)	Ŭ.	**	<u> </u>		С.	70	veut	-C.	C	н	C	н
CH <sub>3</sub>	242-243	66	E-W	247-248	67.81°	6.13	66.89°	6.55	105-110	81	м	129-130	68.81	6.60	69.31	6.78
					62.87 <sup>d</sup>	6.50	61.84*	6.45								
			w	258			64.73	6.38								
CeHa	254-257	71	E-W	260-261		••		••	152-156	96	I	169-170	74.49	5.92	74.41	5.95
			м	225-226		••	!									
CeHICH1	241-243	81	E-W	247-248	70.35 <sup>d</sup>	6.22	70.38°	6.48	7080	96						
			E-W	180			70.54°	6.32								
p-CH;OC4H1CH1	175-178	92.	E	219-220	71.43 <sup>b</sup>	5.95	68.77°	6.69	147-148	82						
					67.79 <sup>d</sup>	6.21										
			E	180-181			68.47°	6.34								
p-NO1C4H4	190-195	88	M-W	196-197						93	м	173~174	64.95	4.88	64.85	4 72
p-(CH <sub>2</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	238-239	85	E-W	242-243	71.64 <sup>0</sup>	6.31	71.61°	6.40	225-227	80						
C4H4CH(CH4)	185-190	62	E-W	230-232	74.95 <sup>5</sup>	6.29	74.91°	6.43								

TABLE I 1234 TETRAHUDRO, & CARBOI INE & CARCOVILIO ACIDE AND METHYL RETERE

W, water; E, ethanol; M, methanol; I, isopropyl alcohol. <sup>b</sup> Calculated for the anhydrous product. <sup>c</sup> Samples were dried at 100° or above *in vacuo* for many hours. <sup>d</sup> Calculated for the monohydrate. <sup>c</sup> Samples were dried *in vacuo* usually at room temperature. <sup>f</sup> The analytical samples evidently contained varying amounts of water. However, either isomeric acid could be converted to the pure completely aromatized derivative (see text).

chloride proved satisfactory for the conversion of the acids to the chlorides, two of which were treated with  $\beta$ -diethylaminoethanol to give the esters (V, R = CH<sub>2</sub> and C<sub>6</sub>H<sub>5</sub>, respectively).

The analogy to the conversion of amides of tryptamine to 3,4-dihydro- $\beta$ -carbolines<sup>14-17</sup> suggested that some of the intermediates of the tryptophan synthesis might be converted directly to  $\beta$ -carboline derivatives. Accordingly, numerous attempts to effect the cyclization of acetyltryptophan and of ethyl  $\alpha$ -acetamino- $\alpha$ -carbethoxy- $\beta$ -(3-indole)-propionate were made. Each substance was heated alone in phenyl ether, with phosphorus oxychloride in benzene, with zinc chloride in acetic anhydride, and with acetaldehyde in water, and the second substance was also heated with phosphorus pentoxide in phenyl ether. The methyl ester of acetyltryptophan also was heated with phosphorus oxychloride in benzene. All these experiments were unsuccessful.

#### Experimental

A. Preparation of the 1,2,3,4-Tetrahydro- $\beta$ -carboline-3-Carboxylic Acids (see Table I).—1-Methyl-1,2,3,4tetrahydro- $\beta$ -carboline-3-carboxylic acid was preparedaccording to the following modification of the method of Jacobs and Craig.<sup>9</sup> In a one-liter flask connected to a Dry Ice condenser with ground-glass joints were placed 26.39 g. of *dl*-tryptophan (0.13 mole), 132 ml. of 1 N sulfuric acid, 350 ml. of water and 70 ml. of freshly-distilled acetaldehyde. This suspension was heated in a water-bath at 50-60° for one hour. The resulting clear solution was then heated directly on the steam-bath for one and one-half hours. The Dry Ice condenser was now removed and heating was continued for four and one-half hours to remove the excess acetaldehyde (hood). The solution was made strongly basic with concentrated ammonium hydroxide, heated for one-half hour on the steambath with decolorizing carbon and filtered. The clear yellow filtrate was concentrated to a volume of about 150 ml., and the resulting mixture was cooled at 5° for nine hours. The white to cream-colored crystals were filtered by suction, washed with cold water and dried at  $80^{\circ}$ . The dry crystals were allowed to stand in the air for thirteen hours until the weight had become constant and the material existed principally as the monohydrate. Concentration of the mother liquor usually caused the separation of additional small quantities of the same material. However, occasionally the material obtained by concentration proved to be higher-melting, and the high-melting isomer (m. p. 258°) was obtained by recrystallization of such samples from water.

1-Phenyl-1,2,3,4-tetrahydro -  $\beta$ -carboline - 3-carboxylic acid was prepared according to the general procedure outlined above. It was not necessary to use a Dry Ice condenser, but it was found helpful to stir the reaction mixture with a Hershberg-type stirrer. The reaction mix-ture with a Hershberg-type stirrer. The reaction mixture consisting of 0.10 mole of tryptophan, 0.11 mole of benz-aldehyde, 100 ml. of 1 N sulfuric acid, 300 ml. of water and 40 ml. of ethanol (95%) was stirred and heated for four heater After the division of 100 ml. of the store of the four hours. After the addition of 100 ml. of concentrated ammonium hydroxide the mixture was heated with decolorizing carbon for twenty minutes, diluted with 50 ml. of concentrated ammonium hydroxide and filtered. The pale yellow solution was cooled in an ice-bath and extracted with two 75-ml. portions of ether. The aqueous The aqueous solution was then concentrated and the product isolated as described for the 1-methyl tetrahydro acid. The main product was a methanol-insoluble portion which could be purified by extraction with methanol and recrystallization from dilute ammonia and then from 50% ethanol. The methanol extracts contained small amounts of the lowmelting isomer, which was purified by recrystallization from methanol.

1-Benzyl-1,2,3,4-tetrahydro- $\beta$ -carboline-3-carboxylic acid was prepared from phenylacetaldehyde by the procedure described for the 2-phenyl tetrahydro acid. Fifty per cent. ethanol was used as the solvent for the reaction, and a reaction time of seventeen hours was necessary. Most of the alcohol was removed by distillation at the end of the reflux period prior to purification and isolation of the product.

The preparation of the 1-homoanisyl-, 1-p-nitrophenyl-, 1-p-dimethylaminophenyl- and 1- $\alpha$ -phenylethyl-1,2,3,4tetrahydro- $\beta$ -carboline-3-carboxylic acids was carried out with essentially the same procedure described for the 1phenyl tetrahydro acid. The bisulfite addition product of homoanisaldehyde was used satisfactorily in place of the free aldehyde.

B. Preparation of the Methyl 1,2,3,4-Tetrahydro- $\beta$ carboline-3-carboxylates (see Table I).—Ten grams of 1 - methyl - 1,2,3,4 - tetrahydro- $\beta$ -carboline - 3 - carboxylic acid was suspended in 75 ml. of dry methanol, and the mixture was saturated with dry hydrogen chloride.

<sup>(14)</sup> Akabori and Saito, Ber., 63, 2245 (1930).

<sup>(15)</sup> Spath and Lederer, ibid., 63, 124, 2102 (1930).

<sup>(16)</sup> Asahina and Osada, Chem. Zentr., 98, I, 1479 (1927).

<sup>(17)</sup> Tatsui, ibid., 99, II, 668 (1928).

After a one-hour reflux period, the solution was concentrated and cooled in an ice-bath. The solid ester hydrochloride was filtered, suspended in water, and treated with an excess of saturated sodium bicarbonate solution. The ester was taken up in ether, and the resulting solution, after drying over magnesium sulfate, was evaporated to yield the crude methyl 1-methyl-1,2,3,4-tetrahydro- $\beta$ carboline-3-carboxylate.

The other esters in this series are not very soluble in ether, so the procedure was modified slightly. After the reflux period (two to three hours) the reaction mixture was cooled and poured onto ice and carefully made basic by the slow addition of ammonium hydroxide. The crude ester was then separated and allowed to stand under cold water for one hour. The solid was then filtered by suction, washed well with water, and dried to constant weight at room temperature in a vacuum desiccator.

It has been found that sulfuric acid can be used in place of hydrogen chloride for these esterifications.

C. Dehydrogenation of the Methyl 1,2,3,4-Tetrahydro- $\beta$ -carboline-3-carboxylates. Preparation of Methyl 1-Methyl- $\beta$ -carboline-3-carboxylate.—In a 250ml. flask equipped with a reflux condenser were placed 15.28 g. of methyl 1-methyl-1,2,3,4-tetrahydro- $\beta$ -carboline-3-carboxylate, 4.16 g. of sulfur and 100 ml. cf dry xylene. This mixture was refluxed for four and one-half hours. The evolution of hydrogen sulfide was noted throughout most of the reflux period. A red crystalline solid precipitated on the walls of the flask. The mixture was cooled overnight at 5° and the pink solid was filtered by suction, washed with 40 ml. of cold xylene and then liberally with low-boiling petroleum ether. The yield was 12.69 g. (85%), m. p. 246-248° (dec.). A sample recrystallized from methanol melted at 245°.

Anal. Caled. for  $C_{14}H_{12}N_2O_2$ : C, 69.96; H, 5.04; N, 11.66. Found: C, 69.86; H, 5.12; N, 11.67.

Methyl 1-Benzyl- $\beta$ -carboline-3-carboxylate was prepared by the same method, but in poor yield; m. p. (after three recrystallizations from *n*-butanol) 237-238°.

Anal. Calcd. for  $C_{20}H_{16}N_2O_2\colon$  C, 75.93; H, 5.10. Found: C, 76.19; H, 5.14.

Methyl 1-Phenyl- $\beta$ -carboline-3-carboxylate.—In а 100-ml. flask equipped with a reflux condenser were placed 5.88 g. of methyl 1-phenyl-1,2,3,4-tetrahydro- $\beta$ carboline-3-carboxylate,<sup>18</sup> 9.91 g. of chloranil, and 80 ml. of purified s-tetrachloroethane. This mixture was heated under reflux for one hour and twenty minutes. The clear dark-colored solution was stored at 5° overnight and the dark crystals which formed were filtered and washed with s-tetrachloroethane, the washings being added to the mother liquor. The solid was discarded. The mother liquor was diluted with a large amount of lowboiling petroleum ether (until no further cloudiness resoluted) and the solid was collected and washed with low-boiling petroleum ether. The dried material was extracted with 225 ml. of boiling 1 N hydrochloric acid in five portions. A small amount of tar remained undissolved. The combined acid extracts were cooled and treated with an excess of solid sodium bicarbonate, and, after cooling for an hour in an ice-bath, the product was filtered, washed well with water, and dried overnight at 80°. The yield was 5.26 g. (91%), m. p. 233-238° (dec.). The melting point could be raised to 252-253° by one recrystallization from n-butyl alcohol. After four such recrystallizations the melting point was constant at 254-255°

Anal. Calcd. for  $C_{19}H_{14}O_2N_2$ : C, 75.48; H, 4.67. Found: C, 75.21; H, 4.76.

(18) The ester prepared from the crude acid or from either of the separated diastereoisomeric acids could be used.

D. Preparation of the  $\beta$ -Carboline-3-carboxylic Acids, their Chlorides and  $\beta$ -Diethylaminoethyl Esters.—The esters were saponified by heating for three to seven hours with 1 N aqueous sodium hydroxide (25 ml. per gram of ester). The solutions were decolorized, cooled and acidified with acetic acid, and allowed to stand in the cold until crystallization was complete. 1-Methyl- $\beta$ -carboline-3-carboxylic acid, m. p. 305-306° after recrystallization from 50% ethanol, apparently retained some water of crystallization even after drying *in vacuo* at 100° for twelve hours.

Anal. Calcd. for  $C_{12}H_{10}N_{2}O_{2}\colon$  C, 69.01; H, 4.45. Found: C, 66.45, 67.17; H, 4.74, 4.91.

1-Phenyl- $\beta$ -carboline-3-carboxylic acid melted at 283.5-284° after recrystallization from aqueous dioxane.

Anal. Calcd. for  $C_{18}H_{12}O_2N_2$ : C, 74.99; H, 4.20. Found: C, 74.86; H, 4.19.

For the preparation of the  $\beta$ -diethylaminoethyl ester of 1-methyl- $\beta$ -carboline-3-carboxylate the crude acid chloride (made by refluxing for one and one-fourth hours a solution of 1 part of the acid with 10 volumes of purified thionyl chloride, distillation of most of the excess reagent at atmospheric pressure and removal of the last traces by distillation at 25 mm. followed by addition and distillation of benzene) was employed. The acid chloride was stirred on a steam-bath with a large excess (9 ml. per gram of acid used in the preparation of the chloride) of freshly distilled diethylaminoethanol for five hours. The mixture was poured on ice, treated with concentrated ammonia, and diluted with water to a volume of ten times that of the diethylaminoethanol. The mixture was allowed to stand in an ice-bath for three hours, after which the solid was collected. It was recrystallized from a mixture of benzene and low-boiling petroleum ether to give a product of m. p. 168.5–170° in 74% yield. Samples purified by recrystallization from benzene-petroleum ether or from alcohol-water appeared to retain water of crystallization. A sample (m. p. 169.5-170°) dried by distillation of most of the benzene from a dilute benzene solution of the substance, followed by precipitation with petroleum ether, was anhydrous.

Anal. Calcd. for  $C_{19}H_{\star3}O_2N_3$ : C, 70.13; H, 7.12. Found: C, 69.92; H, 7.05.

 $\beta$ -Diethylamino 1-phenyl- $\beta$ -carboline-3-carboxylate, m. p. 185–186.5°, was obtained in 86% yield by the same procedure. Recrystallization from benzene and lowboiling petroleum ether raised the melting point to 186– 187°. Traces of colored materials which resisted the action of Darco on the benzene solution could be removed by decolorization of a solution in 95% ethanol. The last traces of water were removed from the analytical sample by distillation with benzene as described above.

Anal. Calcd. for  $C_{24}H_{25}O_{2}N_{3}$ : C, 74.39; H, 6.50. Found: C, 74.17; H, 6.36.

### Summary

The preparation of a number of 1,2,3,4-tetrahydro- $\beta$ -carboline-3-carboxylic acids by the condensation of *dl*-tryptophan with aldehydes is described. Certain carboline-3-carboxylic acids are prepared by dehydrogenation of the aldehydetryptophan condensation products, and the  $\beta$ diethylaminoethyl esters of 1-methyl and 1phenyl- $\beta$ -carboline-3-carboxylic acid are described.

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