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3. 'Alkaloids' in Mammalian Tissues. I. Condensation of L-Dopa and its two Mono-O-methyl Ethers with Formaldehyde and Acetaldehyde[1])

by **A. Brossi, A. Focella,** and **S. Teitel**
Chemical Research Department, *Hoffmann-La Roche Inc.,* Nutley, New Jersey

(29. X. 71)

Zusammenfassung. In der Annahme, dass gewisse Aminosäuren im Gewebe von Säugetieren Vorläufer für «alkaloidische» Tetrahydro-isochinoline sein könnten, wurden L-Dopa und dessen zwei Monomethyläther mit Formaldehyd und Acetaldehyd kondensiert. Die absolute Stereochemie der erhaltenen 1-Methyl-substituierten Tetrahydro-isochinoline wurde durch *Röntgen*-Analyse einer Schlüsselverbindung sichergestellt.

The use of the amino acid L-dopa (**1**) in the treatment of patients with *Parkinson*'s disease has prompted speculations that **1** and its decarboxylation product dopamine [1] undergo chemical reactions in mammalian tissues to form, besides other products, certain tetrahydroisoquinoline 'alkaloids'. The latter may elicit a variety of different pharmacological responses which could account for the side-effects [2]. However, all of these hypotheses have thus far ignored the importance of the stereo-configuration of these tetrahydroisoquinolines. It must be assumed that most of these biochemical reactions are highly selective and will only provide a single optically active entity when new centers of chirality are formed. Further, since enantiomers of related optically

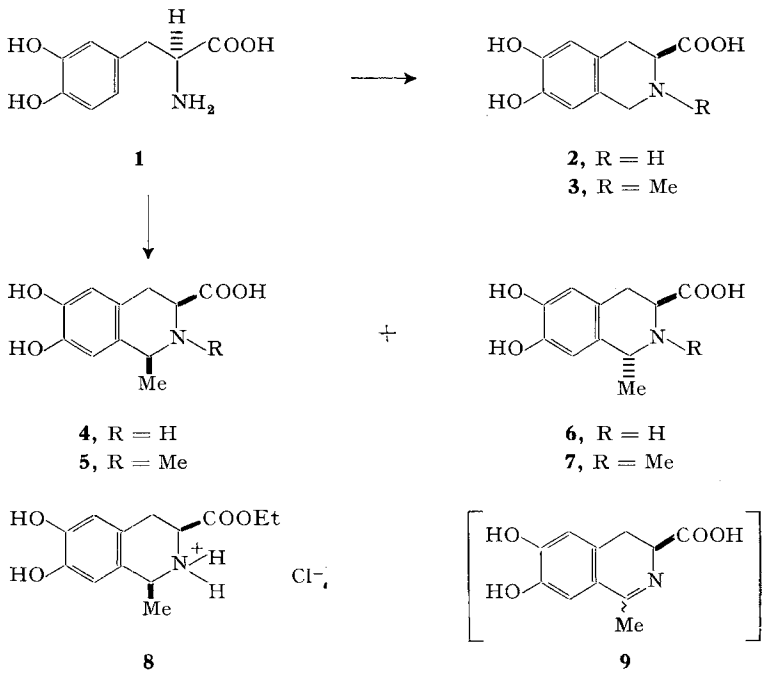
[1]) Presented in part by one of us (*A. B.*) at the 54th Canadian Chemical Conference, Halifax, Nova Scotia, May 31 – June 2, 1971, Abstracts p. 60.

active biogenic amines and amino acids differ markedly in their biological profiles [3], knowledge of the correct stereochemistry of these potential 'alkaloids' synthesized in mammalian tissues is essential.

Based on these considerations, we have undertaken to prepare a number of pure optical isomers of potential tetrahydroisoquinoline 'alkaloids'. We now report, as the first paper of this series, the synthesis, characterization and absolute configuration of the condensation products obtained by reacting L-dopa (**1**) and its two mono-O-methyl ethers (**10** and **12**) with formaldehyde and acetaldehyde, respectively.

Treatment of L-dopa (**1**) (Scheme I) in aqueous suspension with formaldehyde in the presence of mineral acid at room temperature provided the tetrahydroisoquinoline **2**[2]), while catalytic hydrogenation of a mixture of **1** and formaldehyde effected cyclization and N-alkylation to yield the corresponding N-methyl derivative **3**. On the other hand, acid-catalyzed condensation of **1** with acetaldehyde afforded a 95:5 mixture of two isomeric amino acids which was separated by crystallization to give **4** and **6**, respectively. An *X*-ray crystallographic study of the ethyl ester hydrochloride **8**, obtained from the major product **4** by acid-catalyzed esterification, established that the latter is the L-*cis*-acid with the absolute configuration indicated in its formula. The minor product **6** was shown to be the L-*trans*-acid since it was also formed, although in low yield, by careful oxidation of **4** with mercuric acetate followed by reduction with sodium borohydride. The UV. spectrum of the inter-

Scheme I



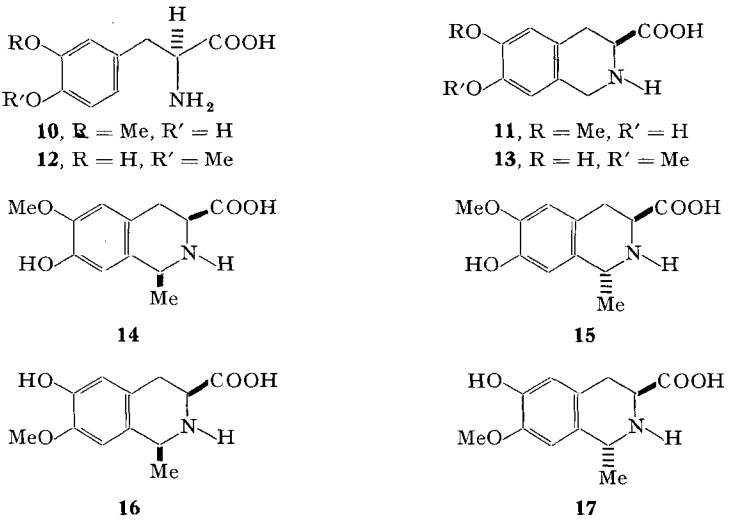
[2]) Its isolation from the seed embryos of *Mucuna mustisiana* and synthesis have been noted in a recent paper [4].

mediate oxidation product **9** – not isolated in pure form[3]) – exhibited a maximum at 355 nm which is in good agreement with a 3,4-dihydroisoquinoline system. Finally, reductive condensation of **4** and **6** with formaldehyde provided the corresponding N-methyl derivatives **5** and **7**.

The condensation of the two mono-O-methyl ethers[4]) (Scheme II) L-3-methoxy-tyrosine (**10**) and its isomer **12** with formaldehyde gave the corresponding tetrahydro-isoquinolines **11** and **13**. Acid-catalyzed cyclization of **10** and **12** with acetaldehyde afforded, as expected, mixtures of the L-*cis*-acids **14** and **16** and the L-*trans*-acids **15** and **17**, respectively, which could be separated by repeated crystallization. The stereochemistry of **14** and **16** was readily established by O-demethylation with 48% hydrobromic acid to yield the L-amino acid **4** of proven absolute configuration. Since the *trans*-isomers **15** and **17** appeared to be unstable in boiling 48% hydrobromic acid, their configurations were assigned by comparison of their physical properties with the *trans*-tetrahydroisoquinoline **6**. For example, the CD. spectra of **6**, **15** and **17** exhibited a stronger negative *Cotton* effect at $\sim$ 280 nm than the corresponding *cis*-isomers **4**, **14** and **16**.

It is noteworthy that the 3-O-methyl ether **10**, due to the lower electron density at the point of ring closure [5], required rather drastic conditions to effect cyclization. It is therefore understandable that **10**, a major metabolite of L-dopa in man [6], accumulates in mammalian tissue.

Scheme II



10, R = Me, R′ = H
12, R = H, R′ = Me
11, R = Me, R′ = H
13, R = H, R′ = Me
14
15
16
17

Experimental

All m.p.'s (uncorrected) were taken in open capillary tubes with a *Thomas-Hoover* melting apparatus. The UV. spectra were measured with a *Cary* recording spectrophotometer Model 14M and the NMR. spectra were obtained with a *Varian* Model HA-100 spectrophotometer using

[3]) Attempts to consume all of **4** by using excess mercuric acetate resulted in complete aromatization.

[4]) Generously provided by our colleagues in Basle, Switzerland.

tetramethylsilane as internal reference. Chemical shifts are reported in δ with the following abbreviations: (*s*) singlet, (*m*) multiplet, (*t*) triplet, (*b*) broad, (*q*) quartet. Optical rotations were measured at 25° with a *Perkin-Elmer* polarimeter Model 141. Rotatory dispersion (ORD.) curves were determined at 23° with a *Durrum-Jasco* spectrophotometer Model 5, using 1 cm, 0.1 cm, or 0.1 mm cells. Circular dichroism (CD.) curves were measured on the same instrument and are expressed in molecular ellipticity units $[\Theta]$. Extracts of products in organic solvents were washed with water and dried over anhydrous sodium sulfate.

(3S)-(−)-6,7-Dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**2**). A solution of 5 g (0.0254 Mol) of L-dopa (**1**), 30 ml (0.39 Mol) of 37% formaldehyde and 300 ml of 0.5 N sulfuric acid was stirred in a nitrogen atmosphere for 24 h, neutralized with 75 ml of 2 N NaOH, and stored at 4°. The white precipitate was filtered, washed with water, and crystallized from water to give 4.6 g (87%) of **2**: m.p. 293–294° (dec.); $[\alpha]_D = -125.91°$ ($c = 1$, 1 N HCl). NMR. ($CD_3OD + DCl$): δ 3.25 (*m*, 2H, $CHCH_2$), 4.31 (*s*, 2H, NCH_2), 4.35 (*m*, 1H, $H_{(3)}$), 6.69 (*s*, 2H, aromatic).

$C_{10}H_{11}NO_4$ (209.2) Calc. C 57.41 H 5.30 N 6.70% Found C 57.63 H 5.48 N 6.64%

(3S)-(−)-6,7-Dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**3**). A mixture of 4.5 g (0.023 Mol) of L-dopa (**1**), 25.5 ml (0.33 Mol) of 37% formaldehyde and 250 ml of water was hydrogenated at 500 psi in the presence of 3 g of 10% Pd/C at 60° until no further hydrogen was absorbed. The catalyst was filtered, washed with 100 ml of methanol and the combined filtrates evaporated under reduced pressure. The residue was crystallized from ethanol and then from water to give 4 g (78%) of **3** as gray crystals: m.p. 253–255°; $[\alpha]_D = -50.57°$ ($c = 1$, 1 N HCl). NMR. [$(CD_3)_2SO$]: δ 2.68 (*s*, 3H, NCH_3), 2.93 (*d*, 2H, $J = 7$ Hz, $CHCH_2$), 3.60 (*t*, 1H, $J = 7$ Hz, $H_{(3)}$), 3.99 (*s*, 2H, NCH_2), 6.52, 6.60 (*s*, 2H, aromatic).

$C_{11}H_{13}NO_4$ (223.2) Calc. C 59.19 H 5.87 N 6.28% Found C 59.17 H 5.63 N 6.32%

(1S,3S)-(−)-6,7-Dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**4**) and *(1R,3S)-(−)-6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid* (**6**). A mixture of 217 g (1.1 Mol) of L-dopa (**1**), 500 ml of acetaldehyde (from a freshly-opened container) and 2 l of 0.5 N sulfuric acid was stirred under N_2 at 50° for 2 h and then at room temperature for 24 h. The white crystals were filtered, washed with water and dried to give 135 g, m.p. 280–282° (dec.). The filtrate was neutralized with 200 ml of 20% NaOH, concentrated to about 1 l, stored at 4° for 24 h, and filtered to give 83 g, m.p. 276–279°. The two crops were combined, suspended in boiling water, filtered and dried to give 217 g (86%) of **4**: m.p. 280–281° (dec.); $[\alpha]_D = -151.5°$ ($c = 1$, 1 N HCl). NMR. ($CD_3OD + DCl$): δ 1.73 (*d*, 3H, $J = 7$ Hz, CH_3), 3.20 (*d*, 2H, $J = 7$ Hz, CH_2), 4.28 (*t*, 1H, $J = 7$ Hz, $H_{(3)}$), 4.58 (*q*, 1H, $J = 7$ Hz, $H_{(1)}$), 6.71, 6.80 (*s*, 2H, aromatic). ORD. ($c = 0.221$, 0.1 N HCl): $[\Phi]_{650} -277°$, $[\Phi]_{589} -342°$, $[\Phi]_{246} -10{,}080°$ (*tr*), $[\Phi]_{229} -2770°$ (*pk*), $[\Phi]_{208} -20{,}160°$ (*tr*); CD. ($c = 0.01$ M, 1 N HCl): $[\Theta]_{310}$ 0, $[\Theta]_{290} -353$, $[\Theta]_{273} -100$, $[\Theta]_{237} -8570$, $[\Theta]_{220} -810$, $[\Theta]_{216} -5640$.

$C_{11}H_{13}NO_4$ (223.2) Calc. C 59.19 H 5.87 N 6.28% Found C 59,05 H 5.65 N 6.47%

The above mother liquors were stored at 4° and the resulting precipitate collected (22 g, m.p. 174–175°) and recrystallized three times from water to give 14 g (5.7%) of **6**: m.p. 212° (dec.); $[\alpha]_D = -74.34°$ ($c = 2$, 1 N HCl). NMR. ($CD_3OD + DCl$): δ 1.62 (*d*, 3H, $J = 7$ Hz, CH_3), 2.9–3.4 (*m*, 2H, CH_2), 4.42 (*d* of *d*, 1H, $J = 6$ and 10 Hz, $H_{(3)}$), 4.65 (*q*, 1H, $J = 7$ Hz, $H_{(1)}$), 6.66 (*s*, 2H, aromatic). ORD. ($c = 0.223$, 0.1 N HCl): $[\Phi]_{650} -137°$, $[\Phi]_{589} -170°$, $[\Phi]_{292} -3750°$ (*tr*), $[\Phi]_{266} -500°$ (*pk*), $[\Phi]_{235} -7500°$ (*tr*), $[\Phi]_{220} -500°$ (*pk*), $[\Phi]_{210} -1750°$; CD. ($c = 0.1$ M, 0.1 N HCl): $[\Theta]_{302}$ 0, $[\Theta]_{282} -3000$, $[\Theta]_{250} -300$, $[\Theta]_{230} -10{,}000$, $[\Theta]_{217} -8000$, $[\Theta]_{204} -22{,}000$, $[\Theta]_{200} -13{,}000$.

$C_{11}H_{13}NO_4$ (223.2) Calc. C 59.19 H 5.87 N 6.28% Found C 58.99 H 6.07 N 6.16%

Alternatively, a mixture of 2.2 g (0.01 Mol) of **4** and 3.4 g (0.011 Mol) of mercuric acetate in 50 ml of acetic acid was stirred at 90° for 4 h, cooled, filtered, and the filtrate evaporated. The residue, a mixture of **4** and the corresponding *3,4-dihydroisoquinoline* **9** [UV., $\lambda_{max}^{2\text{-propanol}}$ (ε): 288 (3600), 355 nm (400)], was dissolved in methanol, treated with 1 g of sodium borohydride, acidified with methanolic hydrochloric acid, diluted with ether and filtered. The filtrate was evaporated, the residue dissolved in water, neutralized with ammonium hydroxide, filtered and concentrated to a low volume. The gray precipitate was collected and crystallized from water to give 35 mg (3%) of **6**, identical in mixed m.p. and optical rotation with **6** obtained as above.

(1 S,3 S)-(–)-6,7-Dihydroxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride (**5** · *HCl*). A mixture of 15 g (0.0675 Mol) of **4**, 45 ml of a 37% formaldehyde solution and 150 ml of methanol was hydrogenated at 400 psi in the presence of 4 g of *Raney* nickel at 40° until no further hydrogen was absorbed. The catalyst was filtered, washed with methanol, and the combined filtrates acidified with methanolic hydrogen chloride and evaporated. The residue was crystallized from 2-propanol to give 10.9 g (58%) of **5** · HCl: m.p. 225–227°; $[\alpha]_D = -44.86°$ ($c = 1$, 1N HCl). NMR. [$(CD_3)_2SO$]: δ 1.65 (*d*, 3H, $J = 7$ Hz, $CHCH_3$), 2.74 (*s*, 3H, NCH_3), 3.17 (*d*, 2H, $J = 8$ Hz, CH_2), 4.5–5.0 (*m*, 2H, $H_{(1)}$ and $H_{(3)}$), 6.70 (*s*, 2H, aromatic), 9.50 (*b*, 4H, $\overset{+}{N}H$ and OH).

$C_{12}H_{15}NO_4 \cdot HCl$ (273.7) Calc. C 52.66 H 5.89 N 5.12% Found C 52.66 H 6.04 N 5.11%

(1 R,3 S)-(–)-6,7-Dihydroxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride (**7** · *HCl*). By the procedure given for the preparation of **5** · HCl, 11 g (0.049 Mol) of **6** afforded 11 g (87%) of **7** · HCl: m.p. 227–228° (from 2-propanol); $[\alpha]_D = -26.94°$ ($c = 2$, 1N HCl). NMR. [$(CD_3)_2SO$]: δ 1.59 (*d*, 3H, $J = 7$ Hz, $CHCH_3$), 2.82 (*s*, 3H, NCH_3), 3.13 (*m*, 2H, CH_2), 4.4–4.8 (*m*, 2H, $H_{(1)}$ and $H_{(3)}$), 6.57 (*s*, 2H, aromatic).

$C_{12}H_{15}NO_4 \cdot HCl$ (273.7) Calc. C 52.66 H 5.89 N 5.12% Found C 52.66 H 6.04 N 5.11%

(1 S,3 S)-(–)-6,7-Dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ethyl ester hydrochloride (**8** · *HCl*). A solution of 10 g of **4** (0.045 Mol) in 130 ml of 10% hydrogen chloride in ethanol was refluxed for 6 h, stored at room temperature overnight, and evaporated under reduced pressure. The residue was crystallized twice from acetic acid to give 9 g as white crystals (70%) of **8** · HCl: m.p. 229–230°; $[\alpha]_D = -110.5°$ ($c = 1$, MeOH). NMR. (CD_3OD): δ 1.34 (*t*, 3H, $J = 7$ Hz, CH_2CH_3), 1.67 (*d*, 3H, $J = 7$ Hz, $CHCH_3$), 3.30 (*m*, 2H, $CHCH_2$), 4.39 (*q*, 1H, $J = 7$ Hz, $H_{(1)}$), 4.43 (*q*, 2H, $J = 7$ Hz, CH_3CH_2), 4.51 (*m*, 1H, $H_{(3)}$), 6.63, 6.71 (*s*, 2H, aromatic). – *X*-ray: orthorhombic crystals, space group $P2_12_12_1$, $a = 11.561$, $b = 7.126$, $c = 16.740$ Å, $Z = 4$, $d_{obs} = 1.35$ g cm^{-3}, μ (Cu$K\alpha$) = 25.0 cm^{-1}, $R = 5.1\%$ (all atoms except hydrogens anisotropic).

$C_{13}H_{17}NO_4 \cdot HCl$	Calc.	C 54.22	H 6.35	N 4.87	Cl 12.22%
(287.7)	Found	,, 54.06	,, 6.31	,, 4.73	,, 12.44%

(3 S)-(–)-7-Hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid monohydrate (**11**). A mixture of 5 g (0.0235 Mol) of L-3-methoxytyrosine (**10**), 6 ml (0.074 Mol) of a 37% formaldehyde solution and 110 ml of 1N sulfuric acid was shaken in a 200 ml glass-lined autoclave under 800 psi of nitrogen pressure at 85–90° for 14 h. The dark solution was decanted from the solids, heated with Norit and filtered. The filtrate was neutralized with 2N sodium hydroxide (~52 ml) and stored. The solids were filtered and crystallized from water to give 1.5 g (27%) of **11**: m.p. 268–269°; $[\alpha]_D = -99.30°$ ($c = 1$, 1N HCl). NMR. (CD_3OD + DCl): δ 3.20 (*m*, 2H, $CHCH_2$), 3.81 (*s*, 3H, OCH_3), 4.32 (*s*, 2H, NCH_2), 4.36 (*m*, 1H, $H_{(3)}$), 6.68, 6.79 (*s*, 2H, aromatic).

$C_{11}H_{13}NO_4 \cdot H_2O$ (241.2) Calc. C 54.77 H 6.27 N 5.81% Found C 54.63 H 6.56 N 5.77%

(3 S)-(–)-6-Hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid monohydrate (**13**). A solution of 5 g (0.0235 Mol) of **12** and 30 ml of 37% formaldehyde in 200 ml of 0.05N sulfuric acid was stirred under a nitrogen atmosphere for 24 h. The white crystals were filtered, washed with water, and dried to give 2.5 g of crude **13** (m.p. 280° dec.). Neutralization of the mother liquor with 50 ml of 2N NaOH gave an additional crop of 1.9 g (m.p. 278–280°). The combined crops were recrystallized from water to give 4.4 g (85%) of **13**: m.p. 290° (dec.); $[\alpha]_D = -117.26°$ ($c = 1$, 1N HCl). NMR. (CD_3OD + DCl): δ 3.20 (*m*, 2H, $CHCH_2$), 3.83 (*s*, 3H, OCH_3), 4.32 (*m*, 1H, $H_{(3)}$), 4.35 (*s*, 2H, NCH_2), 6.67, 6.77 (*s*, 2H, aromatic).

$C_{11}H_{13}NO_4 \cdot H_2O$ (241.2) Calc. C 54.77 H 6.27 N 5.81% Found C 54.50 H 6.41 N 5.73%

(1 S,3 S)-(–)-7-Hydroxy-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid monohydrate (**14**) and *(1 R,3 S)-(–)-7-hydroxy-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid dihydrate* (**15**). A mixture of 10 g (0.047 Mol) of **10**, 40 ml of acetaldehyde and 250 ml of 1N sulfuric acid was shaken in a 300 ml glass-lined autoclave under 800 psi of nitrogen pressure at 90° for 14 h. The solids were filtered, the filtrate heated with 2 g of Norit and filtered. The filtrate was neutralized with 10% sodium hydroxide (about 100 ml), stored, and the resulting solids recrystallized four times from water to give 3.9 g (31.5%) of **14**: m.p. 295° (dec.); $[\alpha]_D = -101.3°$ ($c = 1$, 1:1 of MeOH:0.2N HCl). NMR. (CD_3OD + DCl): δ 1.70 (*d*, 3H, $J = 7$ Hz, $CHCH_3$), 2.9–3.4

(*m*, 2H, CH_2), 3.84 (*s*, 3H, OCH_3), 4.32 (*d* of *d*, 1H, J = 6 and 10 Hz, $H_{(3)}$), 4.57 (*q*, 1H, J = 7 Hz, $H_{(1)}$), 6.77, 6.81 (*s*, 2H, aromatic). ORD. (c = 0.182, 0.1N HCl): $[\Phi]_{600}$ −202°, $[\Phi]_{589}$ −210°, $[\Phi]_{289}$ −1790° (*tr*), $[\Phi]_{284}$ −1685° (*pk*), $[\Phi]_{237}$ −8780° (*tr*), $[\Phi]_{225}$ −2810° (*pk*), $[\Phi]_{212}$ −18,260° (*tr*); CD. (c = 0.0071M, 0.1N HCl): $[\Theta]_{304}$ 0, $[\Theta]_{287}$ −435, $[\Theta]_{259}$ −140, $[\Theta]_{233}$ −7450, $[\Theta]_{221}$ −2950, $[\Theta]_{208}$ −40,740, $[\Theta]_{205}$ −30,910.

$C_{12}H_{15}NO_4 \cdot H_2O$ (255.3) Calc. C 56.45 H 6.71 N 5.48% Found C 56.26 H 6.94 N 5.2%

The combined mother liquors were concentrated to a small volume, treated with Norit, stored at 4°, and the solids collected (4.6 g, m.p. 218–222° dec.) and recrystallized six times from water to give 990 mg (9%) of **15**: m.p. 260–261° (dec.); $[\alpha]_D$ = −55.80° (c = 1, 1:1 of MeOH:1N HCl). NMR. (CD_3OD + DCl): δ 1.63 (*d*, 3H, J = 7 Hz, $CHCH_3$), 3.18 (*m*, 2H, CH_2), 3.81 (*s*, 3H, OCH_3), 4.44 (*m*, 1H, $H_{(3)}$), 4.66 (*q*, 1H, J = 7 Hz, $H_{(1)}$), 6.68, 6.78 (*s*, 2H, aromatic). ORD. (c = 0.1915, 0.1N HCl): $[\Phi]_{600}$ −117°, $[\Phi]_{589}$ −121°, $[\Phi]_{292}$ −2330° (*tr*), $[\Phi]_{271}$ −700° (*pk*), $[\Phi]_{236}$ −8150° (*tr*), $[\Phi]_{222}$ +1160° (*pk*), $[\Phi]_{212}$ −4370° (*tr*), $[\Phi]_{209}$ 0°; CD. (c = 0.0086M, 0.1N HCl): $[\Theta]_{305}$ 0, $[\Theta]_{281}$ −1780, $[\Theta]_{252}$ −210, $[\Theta]_{230}$ −10,360, $[\Theta]_{220}$ −6750, $[\Theta]_{208}$ −26,190, $[\Theta]_{200}$ 0.

$C_{12}H_{15}NO_4 \cdot 2H_2O$ (273.3) Calc. C 52.74 H 7.01 N 5.13% Found C 52.91 H 6.90 N 5.13%

(1 S,3 S)-(−)-6-Hydroxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hemihydrate (**16**) and *(1 R,3 S)-(−)-6-hydroxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hemihydrate* (**17**). A solution of 20 g (0.094 Mol) of L-4-methoxy-*m*-tyrosine (**12**) and 55 ml of acetaldehyde in 500 ml of 0.05N sulfuric acid was stirred under nitrogen at 60° for 2 h and then at room temperature for 20 h. The white precipitate was filtered, washed with water, and dried to give 6.1 g (m.p. 254–255° dec.). The filtrate was neutralized with 250 ml of 1N sodium hydroxide, evaporated to half-volume, and the resulting solid collected to give another 13.8 g, m.p. 250° (dec.). The combined solids (19.9 g) were crystallized from water to give 17.3 g (76.2%) of **16**: m.p. 254–255° (dec.); $[\alpha]_D$ = −135.16° (c = 1, 1:1 of MeOH:1N HCl). NMR. (CF_3COOH): δ 1.96 (*d*, 3H, J = 7 Hz, $CHCH_3$), 3.45 (*d*, 2H, J = 8 Hz, CH_2), 3.96 (*s*, 3H, OCH_3), 4.74 (*m*, 2H, $H_{(1,3)}$), 6.92 (*s*, 2H, aromatic). ORD. (c = 0.246, 0.1N HCl): $[\Phi]_{650}$ −294°, $[\Phi]_{589}$ −372°, $[\Phi]_{235}$ −12,000° (*tr*), $[\Phi]_{228}$ −11,000° (*pk*), $[\Phi]_{205}$ 0° (intersect), $[\Phi]_{198}$ +62,500° (*pk*); CD. (c = 0.01M, 0.1N HCl): $[\Theta]_{292}$ 0, $[\Theta]_{274}$ +320, $[\Theta]_{254}$ 0, $[\Theta]_{229}$ −4800, $[\Theta]_{218}$ −1100, $[\Theta]_{204}$ −66,000, $[\Theta]_{196}$ 0.

$C_{12}H_{15}NO_4 \cdot {}^1/_2H_2O$ (246.3) Calc. C 58.53 H 6.55 N 5.69% Found C 58.84 H 6.55 N 5.69%

The mother liquors, obtained after collecting the second crop of **16**, were concentrated to 200 ml and stored at room temperature overnight. The solids were collected (300 mg, m.p. 232–235°) and recrystallized five times from water to give 70 mg (0.7%) of **17**: m.p. 235–236°; $[\alpha]_D$ = −138.73° (c = 1, 1:1 of MeOH:1N HCl). NMR. (CF_3COOH): δ 1.86 (*d*, 3H, J = 7 Hz, $CHCH_3$), 3.47 (*d*, 2H, J = 8 Hz, CH_2), 3.99 (*s*, 3H, OCH_3), 6.96 (*s*, 2H, aromatic). ORD. (c = 0.216, 0.1N HCl): $[\Phi]_{650}$ −252°, $[\Phi]_{589}$ −307°, $[\Phi]_{292}$ −2770° (*tr*), $[\Phi]_{277}$ −2310° (*pk*), $[\Phi]_{230}$ −10,430° (*tr*), $[\Phi]_{229}$ −9610° (*pk*), $[\Phi]_{212}$ −28,280°; CD. (c = 0.0091M, 0.1N HCl): $[\Theta]_{362}$ 0, $[\Theta]_{283}$ −670, $[\Theta]_{256}$ −140, $[\Theta]_{230}$ −2970, $[\Theta]_{221}$ −1870, $[\Theta]_{206}$ −41,760, $[\Theta]_{199}$ −7140.

$C_{12}H_{15}NO_4 \cdot {}^1/_2H_2O$ (246.3) Calc. C 58.53 H 6.55 N 5.69% Found C 58.44 H 6.32 N 5.68%

Conversion of **14** *and* **16** *into* **4**. A solution of 600 mg (2.45 mMol) of **14** in 25 ml of 48% hydrobromic acid was refluxed for 4 h and evaporated. The residue was dissolved in 20 ml of water and neutralized with ammonium hydroxide to precipitate 450 mg (83%) of **4**, identical in mixed m.p., optical rotation and NMR. with **4** obtained from **1**.

Treatment of **16** in a similar manner also afforded **4**.

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4. Über Pterinchemie

39. Mitteilung [1]

Zur Frage des "aktiven Formaldehyds". Wird durch Formaldehyd-Anlagerung an Tetrahydrofolsäureanaloge ein Imidazolidinring gebildet?

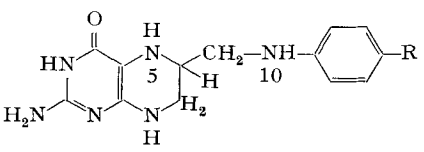
von **M. Viscontini** und **J. Bieri**

Organisch-chemisches Institut der Universität, Rämistrasse 76, CH-8001 Zürich

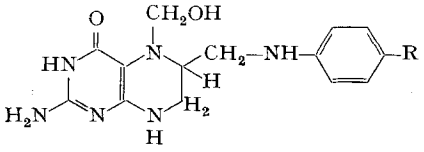
(30. X. 71)

Zusammenfassung. Es werden Versuche mit Tetrahydrofolsäure-Modellsubstanzen unternommen, um die eigentliche Struktur des sogenannten «aktiven Formaldehyds» abzuklären. Alle Addukte der tetrahydrierten Substanzen mit Formaldehyd erweisen sich als Hydroxymethyl- und nicht als Imidazolidin-Derivate. Ob das Additionsprodukt des Formaldehyds mit Tetrahydrofolsäure ebenfalls ein Hydroxymethyl-Derivat ist, bleibt noch abzuklären.

Seitdem entdeckt wurde, dass in Leberextrakten Serin in Gegenwart von Tetrahydrofolsäure (H_4·Folat, Ia), Glycin und Formaldehyd gebildet wird [2] [3], stellt sich die Frage nach der richtigen Struktur des sogenannten «aktiven Formaldehyds» (Anlagerungsprodukt von 1 Mol. HCHO an eine Molekel H_4 · Folat). In ihrer Mitteilung diskutierten *Kisliuk & Sakami* [2] die Bildung von 5-Hydroxymethyl-H_4 · Folat



I



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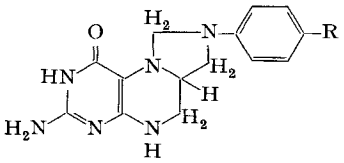
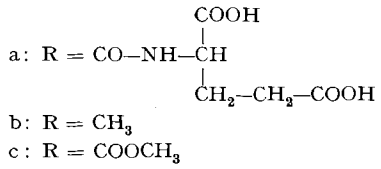


III



a: R = CO–NH–CH(COOH)–CH_2–CH_2–COOH
b: R = CH_3
c: R = $COOCH_3$