208. The Partial O-Demethylation of Aromatic-Substituted 3,4-Dihydroisoquinolines[1])

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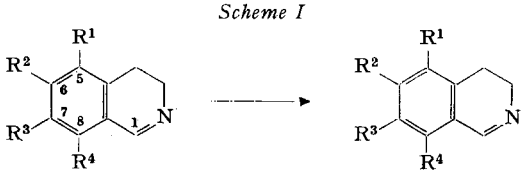
Summary. A detailed study has shown that all possible aromatic dimethoxy-substituted 3,4-dihydroisoquinolines can be partially O-demethylated by controlled acid hydrolysis. Based on the structure elucidation of the monophenols thus obtained, it was established that preferential cleavage occurs at the 5-methoxyl with the 5,6- and 5,8-isomers **1** and **3**, respectively, at the 6-methoxyl with the 6,8-isomer **4**, at the 7-methoxyl with the 5,7-isomer **5**, and at the 8-methoxyl with the 7,8-isomer **2**.

It was previously reported that treatment of 6,7-dimethoxy-3,4-dihydroisoquinoline with mineral acid under carefully controlled conditions effected preferential cleavage of the 7-methoxy group to afford 7-hydroxy-6-methoxy-3,4-dihydroisoquinoline in good yield [1]. More recently this approach was utilized in the facile synthesis of the alkaloid corypalline (7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline) [2]. We have now extended this cleavage study to the remaining five dimethoxy-substituted 3,4-dihydroisoquinolines **1**–**5** and have found that they too could be partially O-demethylated with mineral acid under controlled conditions[2]) to give the monophenols **6**–**10** as major products (Scheme I)[3]).

Scheme I



1 $R^1 = R^2 = OMe$
2 $R^3 = R^4 = OMe$
3 $R^1 = R^4 = OMe$
4 $R^2 = R^4 = OMe$
5 $R^1 = R^3 = OMe$

6 $R^1 = OH$, $R^2 = OMe$
7 $R^3 = OMe$, $R^4 = OH$
8 $R^1 = OH$, $R^4 = OMe$
9 $R^2 = OH$, $R^4 = OMe$
10 $R^1 = OMe$, $R^3 = OH$

Preparation of the dimethoxy dihydroisoquinolines 1–5. All the isomeric dimethoxy-substituted 3,4-dihydroisoquinolines, except the 5,6-isomer (**1**) [3], are new and were prepared by standard methods. The 5,8-isomer **3** was obtained from [2-(2,5-dimethoxy-

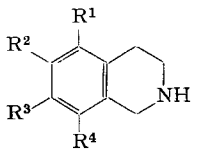
[1]) Presented in part by one of us (*A.B.*) at the 13th Symposium on the Chemistry of Natural Products, Sapporo, Japan, September 25–27, 1967, Symposium Papers pp. 177–186.

[2]) The concentration of mineral acid and substrate as well as the reaction temperature and time influenced the extent of ether cleavage. Conditions were optimized, as visualized by thin layer chromatography, to favour the formation of only one main product. This was possible in all instances except for the hydrolysis of **2** where the formation of a significant amount of the corresponding diphenol could not be avoided.

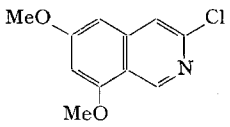
[3]) Unless otherwise indicated, the R substituents are hydrogens.

phenyl)-ethyl]-amine [4] by N-formylation followed by *Bischler-Napieralski* cyclization. The remaining isomers **2**, **4** and **5** were preferably obtained by hypochlorite oxidation [5] of the corresponding tetrahydroisoquinolines **11** [6] and the heretofore unknown 6,8- and 5,7-isomers **13** and **15** (Scheme II)[3]). The latter isomers **13** and **15** were conveniently prepared from the known trimethoxy-substituted precursors **12** [7] and **14** [8], respectively, *via* a modified *Birch* reduction involving the elimination of the middle of three adjacent methoxy groups with sodium in a mixture of liquid ammonia and ethanol [9]. Alternatively, catalytic reduction of the 3-chloro-substituted isoquinoline **16** [10] also afforded the tetrahydroisoquinoline **13** while O-demethoxylation of mescaline (**17**) provided 3,5-dimethoxyphenethylamine (**18**) [11] which was converted by N-formylation and ring closure with phosphorus oxychloride to give the 3,4-dihydroisoquinoline **4** in poor yield.

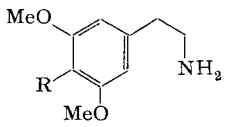
Scheme II



11 $R^3 = R^4 = OMe$
12 $R^2 = R^3 = R^4 = OMe$
13 $R^2 = R^4 = OMe$
14 $R^1 = R^2 = R^3 = OMe$
15 $R^1 = R^3 = OMe$



16



17 R = OMe
18 R = H

Structure proof of the monophenols 6–10. All the monophenols **6–10** were isolated either as crystalline bases or their mineral acid salts, and characterized by physical-chemical methods. The position of the phenolic hydroxyl group was established either by direct comparison with a reference compound prepared by an unequivocal route or else by transformation into a known tetrahydroisoquinoline derivative (Scheme III).

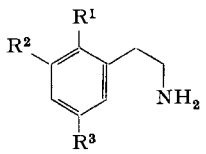
The monophenol **6** was found to be identical with 5-hydroxy-6-methoxy-3,4-dihydroisoquinoline which was prepared from [2-(2-hydroxy-3-methoxyphenyl)-ethyl]-amine (**19**) [12] by N-formylation followed by cyclization with phosphorus oxychloride. In a similar manner, the phenethylamine **20**, obtained from 2-benzyloxy-5-methoxybenzaldehyde [13], was converted to the dihydroisoquinoline followed by O-debenzylation with acid to give 5-hydroxy-8-methoxy-3,4-dihydroisoquinoline, identical with the monophenol **8**. In contrast, the structure of **7** was readily established by reduction with sodium borohydride to afford the known 8-hydroxy-7-methoxy-tetrahydroisoquinoline **21** [8] [14].

To ascertain the position of the phenolic hydroxyl in **9**, this compound was reduced to the tetrahydroisoquinoline **22**, converted into the N-formyl derivative **23** and reacted with 5-chloro-1-phenyl-1*H*-tetrazole to provide the tetrazolyl ether **24**. Hydrogenation of **24** in the presence of palladium removed the tetrazolyl ether group [15] and the resulting monomethoxy N-formyl derivative **25** was reduced with sodium bis-(2-methoxyethoxy)-aluminium hydride to afford a monomethoxy tertiary amine which was identical with 8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**26**)[4])

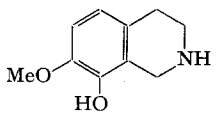
[4]) Kindly provided by our colleague Dr. *F. Schenker* of these Laboratories.

[16] but not with 6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[4]) [17]. Similarily, the monophenol **10** was transformed *via* **27–30** to afford a monomethoxy tetrahydroisoquinoline which was identical with 5-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**31**)[4]) [18] but not with the 7-methoxy isomer[4]) [19]. Further confirmation for the 7-phenolic hydroxyl in **10** was obtained from the non-identity of the corresponding tetrahydroisoquinoline **27** with authentic 5-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline [20].

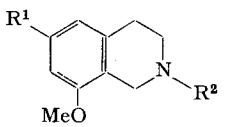
Scheme III



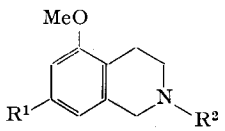
19 $R^1 = OH$, $R^2 = OMe$, $R^3 = H$
20 $R^1 = OC_7H_7$, $R^2 = H$, $R^3 = OMe$



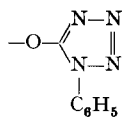
21



22–26



27–31

	R^1	R^2
22	OH	H
23	OH	CHO
24		CHO
25	H	CHO
26	H	Me

Experimental

All melting points (corrected) were taken in open capillary tubes with a *Thomas-Hoover* melting apparatus. All thin layer chromatography employed silica gel G plates which were developed for 15 cm. The Rf values were determined with either solvent system A (100 ethyl acetate:10 methanol:10 ammonium hydroxide), system B (90 acetonitrile:10 ammonium hydroxide) or system C (80 chloroform:20 methanol) and visualized with *Dragendorff*'s reagent. UV. spectra were measured with a *Cary* Model 14M spectrophotometer using ethanol as solvent and the NMR. spectra were recorded on a *Varian* A-60 or HA-100 instrument using tetramethylsilane as internal standard and unless otherwise noted $(CD_3)_2SO$ as solvent. All organic extracts were washed with water and dried over anhydrous sodium sulfate prior to evaporation.

Synthesis of Dimethoxy-Substituted 3,4-Dihydroisoquinolines. – *7,8-Dimethoxy-3,4-dihydroisoquinoline hydrochloride* (**2**·*HCl*). To a solution of 8.8 g (0.04 Mol) of 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**11**) (Lit. [6]: compound **55**, incorrectly named as the 6,7-dimethoxy isomer) in 100 ml of methanol was added over 15 min 21 ml of a 17% solution of freshly prepared sodium hypochlorite. The mixture was stirred at room temperature for 2 h, refluxed for 45 min and evaporated. The residue was diluted with 300 ml of water and extracted with three 100 ml portions of methylene chloride. The combined extracts were evaporated, the residue dissolved in ethanolic hydrogen chloride, evaporated and crystallized from a mixture of 2-propanol

and ether to give 6.1 g (67%) of **2**·HCl: m.p. 143–145°; Rf (system A): 0.95; NMR.: δ 3.05, 3.91 (CH_2CH_2), 3.91, 4.00 (OCH_3-7,8), 7.17, 7.56 (CH-5,CH-6), 9.12 (CH=N); UV., λ_{max}: 224 (16850), 268 (4700), 298 (6760), 380 (1100) nm (ε).

$C_{11}H_{13}NO_2$·HCl (227.68) Calc. C 58.01 H 6.19% Found C 57.96 H 6.61%

5,8-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (**3**·*HCl*). An aqueous solution of 9.4 g (0.04 Mol) of [2-(2,5-dimethoxyphenyl)-ethyl]-amine hydrochloride [4] was rendered alkaline with ammonium hydroxide, extracted with methylene chloride, and the extract evaporated. The residual oil was dissolved in 6.25 g (0.13 Mol) of formic acid, heated at 190° for 3 h, cooled, and 20 ml of phosphorus oxychloride in 25 ml of acetonitrile added. The solution was refluxed for 1 h, evaporated, the residue suspended in 1% sodium hydroxide, and extracted with benzene. The extract was evaporated, the residue dissolved in ethanolic hydrogen chloride, evaporated, and the resulting solid was crystallized from acetonitrile to give 3.2 g (35%) of **3**·HCl: m.p. 185–187°; Rf (system A) 0.72; NMR.: δ 2.94, 3.86 (CH_2CH_2), 3.78, 3.86 (OCH_3-5,8), 7.10, 7.52 (CH-6, CH-8), 8.99 (CH=N); UV., λ_{max}: 215 (12600), 240 (5400) (infl.), 2980 (7900), 409 (3600) nm (ε).

$C_{11}H_{13}NO_2$·HCl (227.68) Calc. C 58.01 H 6.19% Found C 58.17 H 6.43%

6,8-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (**4**·*HCl*). – a) *Preparation from* **13**. To a solution of 2.46 g (0.012 Mol) of O-methylanhalamine (**12**) [7] and 18 ml of ethanol in 200 ml of liquid ammonia was added 1.4 g (0.06 Mol) of sodium in small pieces over 15 min. The mixture was allowed to evaporate at room temperature and the residue partitioned between a mixture of benzene and water. The benzene layer was separated, rendered acidic with ethanolic hydrogen chloride, evaporated, and the residue crystallized from ethanol to give 1.8 g (65%) of 6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**13**·HCl): m.p. 278–280°, Rf (system A) 0.80; NMR. (CH_3OD): δ 3.43, 3.85 (CH_2CH_2), 4.08, 4.10 (OCH_3-6,8), 4.47 (CH_2-1), 6.75 (CH-5,CH-7).

$C_{11}H_{15}NO_2$·HCl (229.70) Calc. C 57.52 H 7.02% Found C 57.29 H 7.09%

Alternatively, a mixture of 2.2 g (0.01 Mol) of 3-chloro-5,8-dimethoxy-isoquinoline (**16**) [10] and 700 mg of sodium acetate in 200 ml of glacial acetic acid was hydrogenated in the presence of 1 g of 10% palladium on carbon at 55–60° and 3 atmospheres until the hydrogen uptake had ceased. The catalyst was filtered, the filtrate evaporated, the residue dissolved in ethanol and rendered acidic with ethanolic hydrogen chloride. The resulting crystals were collected and recrystallized from ethanol to give 1.4 g (61%) of **13**·HCl, identical in m.p. and mixed m.p. and Rf with **13**·HCl obtained from **12**.

An aqueous solution of 6.3 g (0.028 Mol) of **13**·HCl was rendered alkaline with ammonium hydroxide and extracted with methylene chloride. The extract was evaporated, the residue dissolved in 125 ml of methanol, and maintained at 25° as 12.4 ml of 17% sodium hypochlorite was added over 10 min. The mixture was stirred at room temperature for 2 h, 13.6 g of sodium hydroxide added over 10 min, and then refluxed for 45 min. The volatiles were evaporated, the residue suspended in water and extracted with methylene chloride. The extract was acidified with ethanolic hydrogen chloride, evaporated, and the reridue crystallized from a mixture of ethanol and ether to give 4.6 g (73%) of **4**·HCl: m.p. 203–204°, Rf (system A) 0.85; NMR.: δ 3.03, 3.81 (CH_2CH_2), 3.97 (OCH_3-6,8), 6.65 (CH-5,CH-7), 8.78 (CH=N); UV., λ_{max}: 210 (13800), 237 (14480), 320 (11650) (infl.), 345 (13950) nm (ε).

$C_{11}H_{13}NO_2$·HCl (227.68) Calc. C 58.01 H 6.19 N 6.15% Found C 57.99 H 6.16 N 6.03%

b) *Preparation from* **17**. To a solution of 15 g (0.06 Mol) of mescaline hydrochloride (**17**·HCl) in 300 ml of methanol was added 3.3 g (0.06 Mol) of sodium methoxide, the precipitate removed, and the filtrate evaporated. The residue was dissolved in a mixture of 50 ml of ethanol and 800 ml of liquid ammonia, and 10.8 g (0.45 Mol) of sodium added in small pieces over 30 min. The mixture was allowed to evaporate at room temperature, the residue suspended in water, and extracted with benzene. The extract was dissolved in ethanolic hydrogen chloride, evaporated, and crystallized from a mixture of ethanol and ether to give 7.8 g (60%) of [2-(3,5-dimethoxyphenyl)-ethyl]-amine hydrochloride (**18**·HCl): m.p. 155–157° (Lit. [11]: m.p. 156–157°).

An aqueous solution of 7.6 g (0.035 Mol) of **18**·HCl was rendered alkaline with ammonium hydroxide and extracted with benzene. The extract was evaporated, 4.7 ml of formic acid added, heated in a nitrogen atmosphere at 190° for 3 h, dissolved in benzene, washed with 1N hydrochloric acid, and evaporated. The residual oil (6.2 g) was dissolved in 100 ml of acetonitrile, 10 ml of phosphorus oxychloride added, the mixture refluxed for 1 h, and evaporated under reduced pressure.

The residue was suspended in 1% sodium hydroxide, extracted with ethyl acetate, the extract acidified with ethanolic hydrogen chloride, evaporated, and crystallized from a mixture of ethanol and ether to give 3.6 g (45%) of **4**·HCl: m.p. 203–204°, identical in m.p., mixed m.p., thin layer chromatography, and NMR. with **4**·HCl obtained from **13**.

5,7-Dimethoxy-3,4-dihydroisoquinoline hydrochloride (**5**·*HCl*). By the procedure given for the conversion of **17** to **18**, 2.9 g (0.011 Mol) of 5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**14**·HCl), m.p. 273–275° (Lit. [8]: m.p. 268–269°) was treated as the free base with sodium in liquid ammonia to give 1.8 g (71%) of 5,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**15**·HCl): m.p. 284–286° (from ethanol-ether), Rf (system A) 0.40; NMR.: δ 2.85, 3.32 (CH_2CH_2), 3.76, 3.81 (OCH_3-5,7), 4.15 (CH_2-1), 6.40, 6.48 (CH-6, CH-8), 9,62 ($^+NH_2$); UV., λ_{max}: 226 (8680), 283 (2500) nm (ε).

$C_{11}H_{15}NO_2$·HCl (229.70) Calc. C 57.52 H 7.02% Found C 57.27 H 6.99%

By the procedure described for the preparation of **4** from **13**, 2.16 g of **15**·HCl was treated as the free base with sodium hypochlorite to give 1.3 g (61%) of **5**·HCl: m.p. 225–227° (from methanol-ether); Rf (system B) 0.91; NMR.: δ 2.93, 3.88 (CH_2CH_2), 3.85, 3.88 (OCH_3-5,7), 7.03, 7.19 (CH-6, CH-8), 9.15 (CH=N); UV., λ_{max}: 223 (15800), 306 (8060), 385 (1700) nm (ε).

$C_{11}H_{13}NO_2$·HCl (227.68) Calc. C 58.01 H 6.19 N 6.15% Found C 57.87 H 6.14 N 6.16%

Selective O-Demethylation and Structure Proof

5-Hydroxy-6-methoxy-3,4-dihydroisoquinoline hydrochloride (**6**·*HCl*). – a) *Preparation from* **1**. A suspension of 1.9 g (4.4 mMol) of 5,6-dimethoxy-3,4-dihydroisoquinoline picrate (**1**·$C_6H_3N_3O_7$), m.p. 186–188°, Rf (system A) 0.88, (Lit. [3]: m.p. 185°), in a mixture of water and methylene chloride was rendered alkaline with lithium hydroxide, the organic extract evaporated, the residue dissolved in 20 ml of 20% hydrochloric acid, the solution refluxed for 12 h, and evaporated. The residue was crystallized from a mixture of acetonitrile and ether to give 750 mg (80%) of **6**·HCl: m.p. 235–237°; Rf (system A) 0.57; NMR.: δ 3.03, 3.86 (CH_2CH_2), 4.00 (OCH_3), 7.15, 7.53 (CH-7, CH-8), 8.95 (CH=N), 9.50 (OH); UV., λ_{max}: 213 (16700), 243 (5650), 275 (3700) (infl.), 324 (11400) nm (ε).

$C_{10}H_{11}NO_2$·HCl (213.66) Calc. C 56.20 H 5.66% Found C 56.15 H 5.78%

An aliquot of **6**·HCl when converted to the *free base* exhibited m.p. 191–192° (from benzene-ether). $C_{10}H_{11}NO_2$ (177.20) Calc. C 67.78 H 6.26% Found C 68.06 H 6.22%

b) *Preparation from* **19**. A solution of 1.2 g (5.9 mMol) of [2-(2-hydroxy-3-methoxyphenyl)-ethyl]-amine hydrochloride (**19**·HCl) [12] in 50 ml of methanol was neutralized with 320 mg (5.9 mMole) of sodium methoxide, evaporated, and extracted with chloroform. The extract was evaporated, the residual oil dissolved in 0.5 ml of formic acid, and heated at 190° in a nitrogen atmosphere for 3 h. The reaction mixture was dissolved in ethyl acetate, filtered through a short column of silica gel, and the filtrate evaporated. The residual oil (0.5 g) was dissolved in 30 ml of acetonitrile, 1.5 ml of phosphorus oxychloride added, the mixture stirred and refluxed for 1.5 h, and evaporated under reduced pressure. The residue was suspended in water, neutralized with sodium hydrogen carbonate, and extracted with ethyl acetate. The extract was acidified with ethanolic hydrogen chloride, evaporated, and the residue crystallized from a mixture of acetonitrile and ether to give 440 mg (35%) of **6**·HCl, m.p. 234–236°, identical in m.p., mixed m.p., thin layer chromatography, and NMR. with **6**·HCl obtained from **1**. An aliquot when converted to the free base gave no mixed m.p. depression with **6** obtained from **1**.

8-Hydroxy-7-methoxy-3,4-dihydroisoquinoline hydrobromide (**7**·*HBr*). – a) *Preparation from* **2**. A solution of 3 g (15.7 mMole) of 7,8-dimethoxy-3,4-dihydroisoquinoline (**2**), obtained from **2**·HCl in the usual manner, in 30 ml of 62% hydrobromic acid was stirred at 85° for 30 min, diluted with 50 ml of water, evaporated under reduced pressure, and the residue extracted with five 300 ml portions of boiling chloroform[5]). The extracts were evaporated and the residue crystallized from a

[5]) The chloroform insoluble residue was crystallized from a mixture of methanol and ether to give 1.43 g (37%) of 7,8-dihydroxy-3,4-dihydroisoquinoline hydrobromide: m.p. 234–236°; Rf (system A) 0.39; NMR.: δ 2.93, 3.83 (CH_2CH_2), 6.66, 7.17 (CH-5, CH-8), 9.00 (CH=N); UV., λ_{max}: 213 (12700), 240 (7050), 312 (13800), 410 (3040) nm (ε).

$C_9H_9NO_2$·HBr (244.09) Calc. C 44.29 H 4.13% Found C 44.57 H 4.20%

mixture of acetonitrile and ether to give 2.2 g (50%) of **7**·HBr: m.p. 227–229°, Rf (system A) 0.45; Rf (system B) 0.37; NMR.: δ 2.95, 3.85 (CH_2CH_2), 3.89 (OCH_3), 6.80, 7.34 (CH-5, CH-6), 9.01 (CH=N); UV., λ_{max}: 217 (13380), 235 (7940) (infl.), 307 (12410), 398 (3400) nm (ε).

$C_{10}H_{11}NO_2$·HBr (258.12) Calc. C 46.52 H 4.69% Found C 46.60 H 4.95%

b) *Conversion to 8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride* (**21**·*HCl*). A solution of 540 mg (2 mMol) of **7**·HBr in 200 ml of ethanol was hydrogenated in the presence of 100 mg of platinum oxide at 1 atmosphere and 50° until the hydrogen uptake had ceased. The catalyst was filtered, the filtrate evaporated, the residue dissolved in water, neutralized with sodium hydrogen carbonate, and extracted with chloroform. The extract was acidified with ethanolic hydrogen chloride, evaporated, and crystallized from a mixture of ethanol and ether to give 390 mg (90%) of **21**·HCl, m.p. 283–286°, Rf (system B) 0.48, identical in mixed m.p. and thin layer chromatography with an authentic specimen prepared by condensation of 2-hydroxy-3-methoxy-benzaldehyde and aminoacetaldehyde diethylacetal followed by reductive cyclization [8].

An aliquot of **21**·HCl dissolved in water was rendered alkaline with ammonium hydroxide, extracted with chloroform, and the residue crystallized from a mixture of ethanol and ether to give the free *base* **21**, m.p. 180–182°, Rf (system B) 0.48, identical in mixed m.p. and thin layer chromatography with an authentic specimen[6]) of **21** [14].

5-Hydroxy-8-methoxy-3,4-dihydroisoquinoline (**8**). – a) *Preparation from* **3**. An aqueous solution of 400 mg (1.75 mMol) of **3**·HCl was rendered alkaline with ammonium hydroxide, extracted with methylene chloride, and the extract evaporated. The residue was dissolved in 10 ml of 48% hydrobromic acid, refluxed for 7 min, diluted with water, neutralized with sodium hydrogen carbonate and extracted with methylene chloride. The extract was evaporated and the residue crystallized first from ether and then from a mixture of methanol and ether to give 190 mg (61%) of **8**: m.p. 207–209°, Rf (system A) 0.48; NMR.: δ 2.50, 3.60 (CH_2CH_2), 3.80 (OCH_3), 6.86, 6.90 (CH-6, CH-7), 8.45 (CH=N); UV., λ_{max}: 231 (7920), 263 (7150), 342 (4350) nm (ε).

$C_{10}H_{11}NO_2$ (177.20) Calc. C 67.78 H 6.26% Found C 68.01 H 6.10%

b) *Preparation from* [*2-(2-benzyloxy-5-methoxyphenyl)-ethyl*]*-amine* (**20**). A mixture of 24.2 g (0.1 Mol) of 2-benzyloxy-5-methoxy-benzaldehyde [13], 8 ml of nitromethane and 3 g of ammonium acetate in 30 ml of acetic acid was stirred and refluxed for 2 h, and cooled. The crystals were collected, washed with water, dried, and recrystallized from methanol to give 18.7 g (65%) of 2-benzyloxy-5-methoxy-β-nitrostyrene, m.p. 114–116°.

$C_{16}H_{15}NO_4$ (285.29) Calc. C 67.36 H 5.30% Found C 67.62 H 5.37%

A solution of 14.25 g (0.05 Mol) of the above nitrostyrene in 250 ml of tetrahydrofuran was added over 1 h to a stirred and refluxing suspension of 7 g of lithium aluminium hydride in 150 ml of tetrahydrofuran. The mixture was refluxed for 4 h, cooled, ether saturated with water added cautiously, filtered, and the filtrate evaporated. The residue was dissolved in benzene, washed with water, acidified with ethanolic hydrogen chloride, evaporated, and crystallized from a mixture of methanol and ether to give 9.5 g (65%) of **20**·HCl, m.p. 133–135°.

$C_{16}H_{19}NO_2$·HCl (293.78) Calc. C 65.41 H 6.86% Found C 65.20 H 6.98%

An aqueous solution of 1.47 g (5 mMol) of **20**·HCl was rendered alkaline with 10% sodium hydroxide, extracted with ether, the extract evaporated, the residue dissolved in 0.6 ml of formic acid, and heated at 190° in a nitrogen atmosphere for 3 h. The reaction mixture was cooled, diluted with 30 ml of acetonitrile, 2.5 ml of phosphorus oxychloride added, refluxed for 1 h, and evaporated under reduced pressure. The residue was suspended in water rendered alkaline with 20% sodium hydroxide, extracted with ethyl acetate, and the extract evaporated. The residue was dissolved in 20% hydrochloric acid, refluxed for 1 h, cooled, washed with benzene, neutralized with sodium hydrogen carbonate, and extracted with methylene chloride. The extract was evaporated and the residue crystallized from a mixture of methanol and ether to give 370 mg (42%) of **8**, m.p. 207 to 208°, identical in mixed m.p., thin layer chromatography, and NMR. with **8** prepared from **3**.

6-Hydroxy-8-methoxy-3,4-dihydroisoquinoline hydrobromide (**9**·*HBr*). – a) *Preparation from* **4**. An aqueous solution of 8.4 g (36.6 mMol) of **4**·HCl was rendered alkaline with ammonium hydroxide

[6]) Kindly provided by our colleague Dr. *G. Grethe* of these Laboratories.

and extracted with ethyl acetate. The extract was evaporated, the residue dissolved in 150 ml of 48% hydrobromic acid, and refluxed for 45 min. The solution was evaporated under reduced pressure and the residue crystallized from a mixture of methanol and ether to give 5.6 g (72%) of **9**·HBr: m.p. 220–221°, Rf (system A) 0.30, NMR.: δ 3.00, 3.80 (CH_2CH_2), 3.92 (OCH_3), 6.49 (CH-5, CH-7), 8.80 (CH=N), 11.8 (OH, $\overset{+}{N}H$); UV., λ_{max}: 238 (9620), 320 (10500) (infl.), 351 (15000), 380 (6300) nm (ε).

$C_{10}H_{11}NO_2 \cdot HBr$ (258.12) Calc. C 46.52 H 4.69% Found C 46.36 H 4.78%

An aliquot of **9**·HBr in methanol was neutralized with sodium methoxide and the free *base* **9** crystallized from ethyl acetate: m.p. 185–186°.

$C_{10}H_{11}NO_2$ (177.20) Calc. C 67.78 H 6.26% Found C 67.60 H 6.51%

b) *Conversion to 8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride* (**26**·*HCl*). A solution of 4.9 g (19 mMol) of **9**·HBr in 210 ml of methanol was hydrogenated in the presence of 1.5 g of platinum oxide at 3 atmospheres and room temperature until the hydrogen uptake had ceased. The catalyst was filtered, the filtrate evaporated, and the residue crystallized from a mixture of ethanol and ether to give 4.4 g (89%) of 6-hydroxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline hydrobromide (**22**·HBr): m.p. 234–235°; Rf (system A) 0.40; NMR.: δ 2.87, 3.30 (CH_2CH_2), 3.76 (OCH_3), 3.98 (CH_2-1), 6.23, 6.33 (CH-5, CH-7), 9.25 (OH, $\overset{+}{N}H_2$); UV., λ_{max}: 224 (7720), 281 (2100) nm (ε).

$C_{10}H_{13}NO_2 \cdot HBr$ (260.13) Calc. C 46.10 H 5.42% Found C 46.42 H 5.61%

Neutralization of a solution of 4 g (15.4 mMol) of **22**·HBr in 30 ml of water with ammonium hydroxide gave a crystalline precipitate of 2.3 g (83%) of the free *base* **23**, m.p. 196–198°. An aliquot when sublimed exhibited: m.p. 198–200°, Rf (system B) 0.20.

$C_{10}H_{13}NO_2$ (179.21) Calc. C 67.02 H 7.31 N 17.86% Found C 66.88 H 7.42 N 7.89%

A mixture of 2.1 g (11.7 mMol) of **22** and 7 ml of formic acid was maintained at 190° in a nitrogen atmosphere for 4 h, cooled, and evaporated under reduced pressure. The residue was dissolved in ethyl acetate, evaporated, and the solids crystallized from a mixture of ethanol, ether, and petroleum ether to give 1.6 g (66%) of 2-formyl-6-hydroxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**23**): m.p. 167–169°, NMR.: δ 2.73, 3.60 (CH_2CH_2), 3.75 (OCH_3), 4.21 (CH_2-1), 6.17, 6.27 (CH-5, CH-7), 8.13, 8.20 (CHO), 9.23 (OH).

$C_{11}H_{13}NO_3$ (207.22) Calc. C 63.75 H 6.36% Found C 63.48 H 6.49%

A mixture of 1.4 g (6.7 mMol) of **23**, 1.2 g (6.7 mMol) of 5-chloro-1-phenyl-1*H*-tetrazole and 1.04 g (6.7 mMol) of anhydrous potassium carbonate in 50 ml of benzene and 30 ml of dimethylformamide was stirred and refluxed for 24 h, cooled, and filtered. The filtrate was evaporated under reduced pressure, the residue dissolved in benzene, and filtered through a silica gel column. The latter was washed with benzene and eluted with ethyl acetate (400 ml). The eluate was evaporated to leave 2.1 g (88%) of a crystalline residue of 2-formyl-8-methoxy-6-(1-phenyl-1*H*-tetrazol-5-yloxy)-1,2,3,4-tetrahydroisoquinoline (**24**): m.p. 83–85°; NMR.: δ 2.90, 3.73 (CH_2CH_2), 3.90 (OCH_3), 4.45 (CH_2-1), 7.00, 7.15 (CH-5, CH-7), 7.60–8.03 (phenyl), 8.24, 8.34 (CHO).

$C_{18}H_{17}N_5O_3$ (351.36) Calc. C 61.53 H 4.88 N 19.93% Found C 61.22 H 5.19 N 19.97%

A solution of 1.2 g (3.7 mMol) of **24** in 200 ml of ethanol was hydrogenated in the presence of 500 mg of 10% palladium on carbon at 3 atmospheres and room temperature until the hydrogen uptake had ceased. The catalyst was filtered, the filtrate evaporated, the residue dissolved in benzene, filtered through a short column of basic alumina, and the filtrate evaporated. The crystalline residue (450 mg, 83%) of 2-formyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**25**) exhibited m.p. 74–76°; NMR.: δ 2.95, 3.60 (CH_2CH_2), 3.79 (OCH_3), 4.40 (CH_2-1), 6.60–6.91, 7.15 (CH-5, CH-6, CH-7), 8.11, 8.20 (CHO).

$C_{11}H_{13}NO_2$ (191.22) Calc. C 69.09 H 6.85% Found C 69.37 H 6.85%

A mixture of 300 mg (1.57 mMol) of **25** and 2.5 ml of a 70% solution of sodium bis-(2-methoxyethoxy)-aluminium hydride in benzene and diluted with 40 ml of tetrahydrofuran was stirred and refluxed 3 h, cooled, and 5 ml of water was added. The precipitate was filtered, the filtrate evaporated, the residue dissolved in benzene, and acidified with ethanolic hydrogen chloride. The crystals were collected and recrystallized from a mixture of methanol and ether to give 245 mg (73%) of 8-

methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**26**·HCl): m.p. 218–220°; Rf (system C) 0.64; NMR.: δ 2.86 ($\overset{+}{N}CH_3$), 3.10, 3.35 (CH_2CH_2) 3.79 (OCH_3), 4.13 (CH_2-1), 6.80, 6.87, 7.25 (CH-5, CH-6, CH-7); identical in mixed m.p., thin layer chromatography, and NMR. with an authentic specimen[4]) of **26**·HCl [16]; mixed m.p. 157–164° with an authentic specimen[4]) of 6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[7]) [17].

$C_{11}H_{15}NO \cdot HCl$ (213.71) Calc. C 61.81 H 7.55% Found C 61.77 H 7.70%

7-Hydroxy-5-methoxy-3,4-dihydroisoquinoline hydrobromide (**10**·*HBr*). – a) *Preparation from* **5**. An aqueous solution of 6.3 g (27.8 mMol) of **5**·HCl was neutralized with ammonium hydroxide, extracted with methylene chloride, and the extract evaporated. The residue was dissolved in 70 ml of 48% hydrobromic acid, the solution heated at 120–125° for 40 min, cooled, diluted with 50 ml of water, and extracted with chloroform. The extract was washed with 10% sodium hydroxide, acidified with ethanolic hydrogen chloride, evaporated, and the residue crystallized from a mixture of ethanol and ether to give 2.34 g (37%) of recovered **5**·HCl. The aqueous phase from the reaction mixture was evaporated and the residue crystallized from a mixture of methanol and ether to give 3.4 g (74% overall) of **10**·HBr: m.p. 246–248°; Rf (system B) 0.57; NMR.: δ 2.88 (CH_2-4), 3.80 (OCH_3), 3.85 (CH_2-3), 6.89, 6.95 (CH-6, CH-8), 9.16 (CH=N), 10.1 (OH or $\overset{+}{N}H$); UV., λ_{max}: 223 (18100), 261 (4200), 303 (6300), 385 (1200) nm (ε); λ_{max} in 0.1N KOH: 237 (23400), 273 (4950), 350 (2400) nm (ε).

$C_{10}H_{11}NO_2 \cdot HBr$ (258.12) Calc. C 46.52 H 4.69% Found C 46.72 H 4.93%

b) *Conversion to 5-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride* (**31**·*HCl*). By the transformations given for the conversion of **9** to **26**, the following were obtained:

7-Hydroxy-5-methoxy-1,2,3,4-tetrahydroisoquinoline hydrobromide (**27**·*HBr*): 92% yield from **10**; m.p. 272–274° (from methanol-acetonitrile-ether); Rf (system B) 0.40; NMR.: δ 2.68, 3.29 (CH_2CH_2), 3.71 (OCH_3), 4.11 (CH_2-1), 6.18, 6.33 (CH-6, CH-8), 9.27 (OH, $\overset{+}{N}H_2$); UV., λ_{max}: 225 (7830), 282 (2700) nm (ε); mixed m.p. 224–229° with 5-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide[8]) [20].

$C_{10}H_{13}NO_2 \cdot HBr$ (260.13) Calc. C 46.10 H 5.42% Found C 46.38 H 5.43%

2-Formyl-7-hydroxy-5-methoxy-1,2,3,4-tetrahydroisoquinoline (**28**): 87% yield from **27**; m.p. 158–160° (from ethanol-ether-petroleum ether); NMR.: δ 2.50, 3.57 (CH_2CH_2), 3.70 (OCH_3), 4.41 (CH_2-1), 6.17, 6.24 (CH-6, CH-8), 8.12, 8.16 (CHO), 9.26 ($\overset{+}{N}H$, OH).

$C_{11}H_{13}NO_3$ (207.22) Calc. C 63.75 H 6.36 N 6.76% Found C 63.61 H 6.51 N 6.63%

*2-Formyl-5-hydroxy-7-(1-phenyl-1*H*-tetrazol-5-yloxy)-1,2,3,4-tetrahydroisoquinoline* (**29**): 94% yield from **28**; m.p. 145–147° (from ethyl acetate-ether); NMR.: δ 2.66, 3.65 (CH_2CH_2), 3.75 (OCH_3), 4.54 (CH_2-1), 6.95, 7.05 (CH-6, CH-8), 7.50–8.00 (phenyl), 8.16, 8.21 (CHO).

$C_{18}H_{17}N_5O_3$ (351.36) Calc. C 61.53 H 4.88 N 19.93% Found C 61.77 H 4.89 N 19.92%

2-Formyl-5-methoxy-1,2,3,4-tetrahydroisoquinoline (**30**): 88% from **29** as an oil; NMR.: δ 2.59, 3.60 (CH_2CH_2), 3.76 (OCH_3), 4.52 (CH_2-1), 6.50–6.90, 7.03 (CH-6, CH-7, CH-8), 8.14, 8.19 (CHO).

5-Methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**31**·*HCl*): 79% yield from **30**; m.p. 224–226° (from methanol-ether); Rf (system C) 0.64; NMR.: δ 2.83 ($\overset{+}{N}CH_3$), 2.91, 3.46 (CH_2CH_2), 3.79 (OCH_3), 4.28 (CH_2-1) 6.85, 6.90, 7.25 (CH-6, CH-7, CH-8); identical in mixed m.p., thin layer chromatography, and NMR. with an authentic specimen[4]) of **31**·HCl [18]; mixed m.p. 184–187° with an authentic specimen[4]) of 7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride[9]) [19].

$C_{11}H_{15}NO \cdot HCl$ (213.71) Calc. C 61.81 H 7.55% Found C 61.92 H 7.56%

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[7]) M.p. 167–169°; Rf (system C) 0.46; NMR.: δ 2.82 ($\overset{+}{N}CH_3$), 3.10, 3.35 (CH_2CH_2), 3.73 (OCH_3), 4.12 (CH_2-1), 6.75, 6.80, 7.06 (CH-5, CH-7, CH-8).

[8]) M.p. 253–255°; Rf (system B) 0.37; NMR.: δ 2.82, 3.45 (CH_2CH_2), 3.67 (OCH_3), 4.16 (CH_2-1), 6.26, 6.36 (CH-6, CH-8), 9.03 ($\overset{+}{N}H_2$), 9.65 (OH).

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[9]) M.p. 212–214°; Rf (system C) 0.55; NMR.: δ 2.81 ($\overset{+}{N}CH_3$), 3.01, 3.39 (CH_2CH_2), 3.71 (OCH_3), 4.26 (CH_2-1), 6.75, 6.84, 7.15 (CH-5, CH-6, CH-8), 11.50 ($\overset{+}{N}H$).

209. Die Kristallstruktur von 2,4-Diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidin-1-oxid-dihydrat

(Ein Metabolit von Trimethoprim)

von **W. E. Oberhänsli**

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Herrn Dr. *O. Isler* zum 60. Geburtstag gewidmet.

(31. VIII. 70)

Summary. The crystal structure of the title compound has been determined by threedimensional *X*-ray diffraction methods. The crystals belong to the space group $P\bar{1}$ with cell constants

a = 7.851 Å	b = 10.703 Å	c = 10.399 Å
α = 100.06°	β = 97.38°	γ = 75.77°

The structure has been refined to an *R*-value of 4.0%.
The geometry of the molecule and the hydrogen bonding in the crystal are discussed.

Einführung. – Trimethoprim = 2,4-Diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidin ist eine antibakterielle Verbindung und Bestandteil des Chemitherapeutikums BACTRIM®.