This work is part of project No. SR 2.120.69 of the *Schweizerischer Nationalfonds*. Financial support by *CIBA-GEIGY S.A.*, Basel, is gratefully acknowledged. Finally we wish to thank *SANDOZ AG* for the gift of computer time.

Appendix. Table 4 lists the analysis of the vibrational fine structure of bands ②, ③ and ④.

The numbering of the spacings refers to Fig. 3. The spacings have been measured in arbitrary, units, which have been converted into the values in eV of Table 4 by multiplication with a scale factor.

The results of the least-squares analysis are given, for convenience, in cm^{-1}. The *Student-t*-values are those for $P = 0.1$ *i.e.* for 90 percent confidence limit.

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165. Synthesis and Absolute Configuration of Cryptostylines I, II, and III

by **A. Brossi** and **S. Teitel**

Chemical Research Department, *Hoffmann-La Roche Inc.*, Nutley, New Jersey 07110

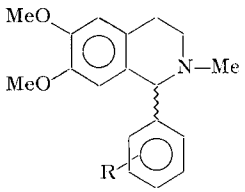
Dedicated to Professor Dr. *H. H. Inhoffen* on the occasion of his 65th birthday

(5. VI. 71)

Zusammenfassung. Die Darstellung der drei optisch aktiven natürlichen Alkaloide Cryptostyline I, II und III aus *Cryptostylis fulva Schltr.* und ihrer drei unnatürlichen Antipoden wird beschrieben. Es wird gezeigt, dass die drei natürlichen Cryptostyline *S*-Konfiguration besitzen. Die berichtete leichte Racemisierbarkeit der natürlichen Cryptostyline wird auf optische Unreinheit der ursprünglichen Präparate zurückgeführt.

The optically active alkaloids cryptostyline I, II, and III isolated by *Leander et al.* from *Cryptostylis fulva Schltr.* (*Orchidaceae*) are substituted 1-phenyl-tetrahydroisoquinolines whose basic chemical structures (shown below) have been elucidated by physical methods and verified by a straightforward synthesis of their (±)-isomers [1].

The first preparation of the three optically active alkaloids and their 'unnatural' enantiomers is described; furthermore, the natural cryptostylines I, II, and III are shown to possess the *S* configuration (structures **5a, b, c**).



(±)-Cryptostyline I, R = 3,4-(OCH_2O); II, R = 3,4-$(OMe)_2$; III, R = 3,4,5-$(OMe)_3$

Optical Resolution of (±)-*Norcryptostylines.* The three (±)-norcryptostylines could easily be resolved by the following conventional techniques. The secondary amines **2a,b,c**, obtained from the known 3,4-dihydroisoquinolines **1a,b,c** [1] by sodium borohydride reduction, were resolved with (−)-diacetone-2-keto-L-gulonic acid[1]) (DAG) [2] to afford, upon neutralization of the optically pure DAG salts the levorotatory bases (−)-**3a** and (−)-**3c** and the dextrorotatory base (+)-**4b**[2]). The ORD. spectrum of (+)-**4b** exhibited *Cotton* effects opposite to those of (−)-**3a** and (−)-**3c** thus indicating that (+)-**4b** belongs to the enantiomeric series. To obtain the remaining three antipodes, the DAG salt mother liquors from (−)-**3a** and (+)-**4b** were rendered alkaline and the resulting bases treated with (−)- and (+)-tartaric acid, respectively. The crystalline tartrates thus obtained were neutralized to provide the corresponding dextrorotatory base (+)-**4a** and the levorotatory base (−)-**3b**. The remaining enantiomer (+)-**4c** was directly crystallized from an ether solution of the neutralized mother liquors of the DAG salt of (−)-**3c**. Thus, all six optically active norcryptostylines (−)-**3a,b,c** and (+)-**4a,b,c** could easily be prepared and classified on the basis of their optical behaviour.

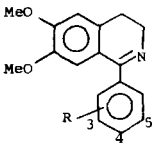
Synthesis and Optical Purity of Cryptostylines I, II, and III. Reductive N-methylation of the secondary (−)-bases **3a,b,c** afforded the tertiary (+)-bases **5a,b,c** which were readily purified by filtration through an aluminum oxide column. Similarly, the secondary (+)-bases **4a,b,c** were converted into the tertiary (−)-enantiomers **6a,b,c**. Each of the crystalline tertiary amines was characterized in the form of its hydrobromide which was reconverted into the free base. The latter was identical in specific rotation with the original base and thus indicated high optical purity. The ORD. and CD. spectra of **5a,b,c**, exhibiting two negative *Cotton* effects at ~290 and 210 nm and two positive effects in the 275 and 240 nm region, were the mirror images of the corresponding spectra of the enantiomers **6a,b,c**.

The physical and optical data obtained for crystalline **5a** and **5b** agree well with those reported for cryptostyline I and II respectively, whereas the specific rotation of **5c** is significantly higher than that given for cryptostyline III. This latter discrepancy suggests that so-called natural cryptostyline III is probably optically impure. Indeed, crystallization of an artificial mixture of 5 parts of (+)-**5c** and 1 part of (−)-**6c** from

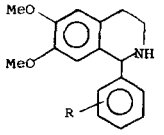
[1]) Recently used to resolve an intermediate in the synthesis of the alkaloid cherylline [3].

[2]) The (+) or (−) signs refer to the $[\alpha]_D^{25}$ values of the crystalline bases measured in 1% methanolic solution.

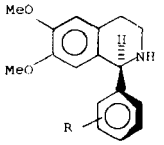
ether afforded a product with properties similar to that reported for natural cryptostyline III[3]). Furthermore, optically pure **5a** could not be racemized by boiling in ether nor by treatment with 1 N mineral acid or 1 N alcoholic sodium hydroxide. This also indicates that *Leander et al.* who reported the facile racemization of cryptostyline I by boiling in ether [1] have thus very probably separated the less soluble (±)-modification (**5a**:**6a** = 1:1) from their initial mixture of enantiomers.



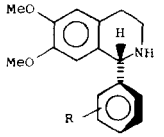
1a, b, c



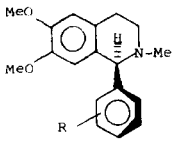
2a, b, c



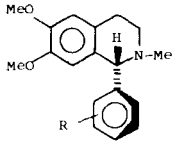
3a and DAG salt
3b and (−)-tartrate
3c and DAG salt



4a and (+)-tartrate
4b and DAG salt
4c



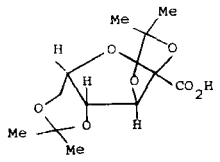
5a, b, c



6a, b, c

a, R = 3,4-(OCH_2O);
b, R = 3,4-$(OMe)_2$;
c, R = 3,4,5-$(OMe)_3$

DAG =

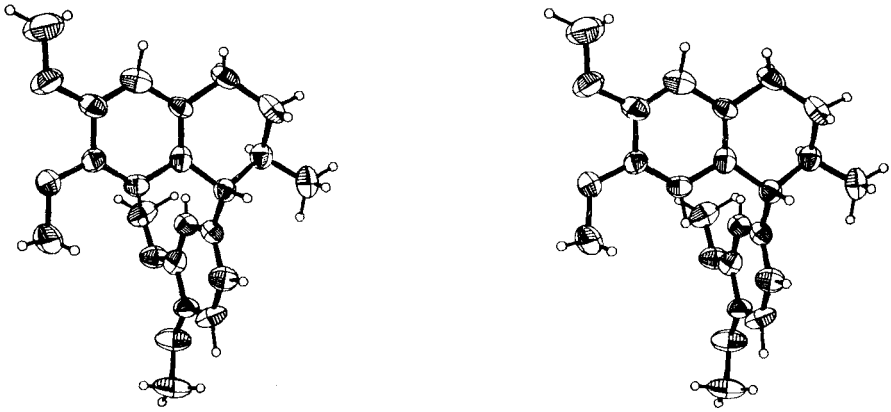


Absolute Configuration of Cryptostylines I, II, and III. The hydrobromide of unnatural cryptostyline II (**6b** · HBr) crystallizes from ethanol in the orthorhombic space group $P\,2_12_12_1$ with cell dimensions $a = 10.183$, $b = 12.314$, $c = 16.435$ Å. A single crystal *X*-ray analysis of this salt was carried out and refined to an *R* value of 3.3%[4]). The stereo drawing below illustrates the absolute configuration of the anion of **6b** thus determined and shows that the aromatic ring of the 1-substituent lies below and almost perpendicular to the plane of the aromatic ring in the isoquinoline moiety and that the two methoxy groups in the 3,4-position are directed towards the far side.

[3]) A similar behaviour was observed with the alkaloid (+)-calycotomine, also isolated from natural sources in optically impure form [4].

[4]) The *X*-ray study of **6b** · HBr was performed by Dr. *J. F. Blount* of our Physical Chemistry Department who will publish the details elsewhere.

This creates a sterically favourable arrangement for the entire molecule. Based on this analysis, unnatural cryptostyline II (**6b**) as well as the analogues **6a** and **6c** possess the *R* configuration. It therefore follows that the natural cryptostylines I (**5a**), II (**5b**), and III (**5c**) have *S* configuration[5]).



Stereoscopic view of the anion of **6b** (*Unnatural Cryptostyline II*)

Experimental Part

All m. p.'s (corrected) were taken in open capillary tubes with a *Thomas-Hoover* apparatus. The UV. spectra were measured in 2-propanol with a *Cary* recording spectrophotometer Model 14M. NMR. spectra were obtained with a *Varian* Model HA-100 spectrophotometer, using $CDCl_3$ as solvent and tetramethylsilane as internal reference. Chemical shifts are reported in δ with the following abbreviations: (*s*) singlet, (*m*) multiplet, (*t*) triplet, (*b*) broad. Optical rotations were measured at 25° using 1% solutions with a *Perkin-Elmer* polarimeter Model 141. Rotatory dispersion curves (ORD.) 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 [Θ]. Extracts of products in organic solvents were washed with water and dried over anhydrous sodium sulfate.

1. Synthesis of (±)-Norcryptostylines. – (±)-*6,7-Dimethoxy-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline*[6]) (**2a**). To a stirred solution of 87 g (0.28 mol) of 6,7-dimethoxy-1-(3,4-methylenedioxyphenyl)-3,4-dihydroisoquinoline (**1a**) [1] in 800 ml of methanol at 15–20°, 41 g of sodium borohydride was added over 0.5 h. After stirring at 25° for 3 h, the reaction mixture was evaporated, the residue suspended in water and extracted with methylene chloride. The organic extract was evaporated and the residue crystallized from benzene to give 70.4 g (80%) of **2a**: m.p. 137–138°; UV., λ_{max} (ε): 286 (8000), 235 nm (11500) (infl.).

$C_{18}H_{19}NO_4$ (313.34) Calc. C 68.99 H 6.11 N 4.47% Found C 68.78 H 6.14 H 4.50%

(±)-*6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline*[7]) (**2b**). As for **2a**, 65.6 g (0.2 mol) of 6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-3,4-dihydroisoquinoline (**1b**) [1] was treated with 25 g of sodium borohydride and the reaction product crystallized from 2-propanol to give 40 g (60%) of **2b**: m.p. 104–106°; UV., λ_{max} (ε): 281 (6680), 230 nm (18000) (infl.).

$C_{19}H_{23}NO_4$ (329.38) Calc. C 69.28 H 7.04% Found C 69.37 H 7.40%

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[5]) Recently the absolute configuration of the natural cryptostylines was suggested by an indirect comparison with optically active model substances [5]. The results of this study were inconclusive however.

[6]) First prepared in these laboratories by Dr. *J. Finkelstein.*

[7]) First prepared in these laboratories by Dr. *W. Wenner.*

(±)-6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline[7] (**2c**). As for **2a**, reduction of 89 g (0.25 mol) of 6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)-3,4-dihydroisoquinoline (**1c**) [1] with 36 g of sodium borohydride afforded, after crystallization from ether, 69.5 g (77%) of **2c**: m.p. 108–110°; UV., λ_{max} (ε): 283 (4040), 235 (15600) (infl.).

$C_{20}H_{25}NO_5$ (359.41) Calc. C 66.83 H 7.01 N 3.90% Found C 66.42 H 6.94 N 3.80%

2. Optical Resolution of (±)-Norcryptostylines. – *(−)-(1S)-6,7-Dimethoxy-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline* (**3a**) *and (−)-diacetone-2-keto-L-gulonate* (**3a** · DAG). A solution of 40 g (0.128 mol) of **2a** and 38 g (0.13 mol) of (−)-diacetone-2-keto-L-gulonic acid hydrate [2] in 300 ml of ethanol was stored at room temperature overnight. The crystals formed were filtered off (the filtrate was used for the preparation of **4a**) and recrystallized from 200 ml of ethanol to give 22.5 g (60% based on 0.064 mol) of **3a** · DAG: m.p. 204–205°; $[\alpha]_D = -16.3°$ (MeOH).

$C_{18}H_{19}NO_4 \cdot C_{12}H_{18}O_7$ (587.60) Calc. C 61.32 H 6.35 N 2.39%
Found ,, 61.11 ,, 6.28 ,, 2.32%

The base liberated from an aqueous solution of 21.7 g (0.037 mol) of **3a**·DAG with 10% sodium hydroxide was extracted with ethyl acetate, the organic extract evaporated and the residue crystallized from 30 ml of 2-propanol to give 11 g (95%) of **3a**: m.p. 122–123°; $[\alpha]_D = -23.0°$ ($CHCl_3$); NMR.: δ 1.93 (*s*, 1H, NH); 2.60–3.30 (*m*, 4H, CH_2CH_2); 3.60, 3.82 (*s*, 6H, 2 OCH_3); 4.92 (*s*, 1H, $H_{(1)}$); 5.90 (*s*, 2, OCH_2O); 6.25, 6.59 (*s*, 2H, $H_{(5,8)}$); 6.72 (*s*, 3H, $H_{(2',5',6')}$); ORD. (*c* = 0.313, MeOH): $[\Phi]_{700} = -70°$, $[\Phi]_{589} = -112°$, $[\Phi]_{297} = -11100°$ (*tr*), $[\Phi]_{292} = 0°$, $[\Phi]_{283} = +17700°$ (*pk*), $[\Phi]_{271} = 0°$, $[\Phi]_{264} = -3300°$ (*tr*), $[\Phi]_{254} = 0°$, $[\Phi]_{247} = +2400°$ (*pk*), $[\Phi]_{243} = 0°$, $[\Phi]_{230} = -17500°$ (*sh*), $[\Phi]_{212} = +35000°$ (*tr*); CD. (*c* = 0.01 M, MeOH): $[\Theta]_{305} = 0$, $[\Theta]_{293} = -18800$, $[\Theta]_{283} = 0$, $[\Theta]_{276} = +10600$, $[\Theta]_{256} = +1800$, $[\Theta]_{240} = +13000$, $[\Theta]_{231} = 0$, $[\Theta]_{206} = -140000$.

$C_{18}H_{19}NO_4$ (313.34) Calc. C 68.99 H 6.11 N 4.41% Found C 69.02 H 6.22 N 4.35%

(+)-(1R)-6,7-Dimethoxy-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**4a**) *and (+)-tartrate*. The ethanol mother liquor obtained from the crystallization of crude **3a** · DAG was evaporated, the residue dissolved in water, rendered alkaline with 10% sodium hydroxide, extracted with ethyl acetate and the extract evaporated. The residual oil (27.8 g) and 15 g (0.1 mol) of (+)-tartaric acid were dissolved in 400 ml of methanol and the solution stored at room temperature overnight. The resulting crystals (24 g) were filtered off and recrystallized from 400 ml of water to give 12 g (40% based on 0.064 mol present in **2a**) of **4a** · (+)-tartrate: m.p. 236–238°; $[\alpha]_D = +57.8°$ (H_2O).

$C_{18}H_{19}NO_4 \cdot C_4H_6O_6$ (463.43) Calc. C 61.01 H 5.44 N 3.02%
Found ,, 61.16 ,, 5.72 ,, 3.43%

Conversion of 9.2 g (0.02 mol) of **4a** · (+)-tartrate to the base followed by crystallization from 30 ml of 2-propanol afforded 6 g (96%) of **4a**: m.p. 123–124°; $[\alpha]_D = +23.0°$ ($CHCl_3$); in NMR. identical with **3a**; in ORD. and CD. mirror image of **3a**.

$C_{18}H_{19}NO_4$ (313.34) Calc. C 68.99 H 6.11 N 4.47% Found C 69.23 H 6.17 N 4.42%

(+)-(1R)-6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**4b**) *and its (−)-diacetone-2-keto-L-gulonate* (**4b** · DAG). A mixture of 33 g (0.1 mol) of **2b** and 29.2 g (0.1 mol) of (−)-diacetone-2-keto-L-gulonic acid hydrate was dissolved in 250 ml of boiling 2-propanol and stored at room temperature overnight. The crystals were filtered off (the filtrate was used for the preparation of **3b**) and recrystallized from 250 ml of 2-propanol to give 15 g (50% based on 0.05 mol) of **4b** · DAG: m.p. 126–127°; $[\alpha]_D = -3.0°$ (MeOH).

$C_{19}H_{23}NO_4 \cdot C_{12}H_{18}O_7$ (603.65) Calc. C 61.68 H 6.85 N 2.32%
Found ,, 61.38 ,, 6.89 ,, 2.29%

In the usual manner 14 g (0.024 mol) of **4b** · DAG was converted into the base and the latter crystallized from 2-propanol to give 7.5 g (95%) of **4b**: m.p. 114–115°; $[\alpha]_D = +33.5°$ ($CHCl_3$); NMR.: δ 1.85 (*s*, 1H, NH); 2.60–3.30 (*m*, 4H, CH_2CH_2); 3.64, 3.81, 3.86, 3.86 (*s*, 12H, 4 OCH_3); 4.97 (*s*, 1H, $H_{(1)}$); 6.27, 6.62 (*s*, 2H, $H_{(5,8)}$); 6.80 (*s*, 3H, $H_{(2',5',6')}$); ORD. (*c* = 0.239, MeOH): $[\Phi]_{700} = +107°$, $[\Phi]_{589} = +160°$, $[\Phi]_{294} = +9980°$ (*pk*), $[\Phi]_{289} = 0°$, $[\Phi]_{280} = -20640°$ (*tr*), $[\Phi]_{267} = 0°$, $[\Phi]_{263} = +2060°$ (*pk*), $[\Phi]_{258} = 0°$, $[\Phi]_{24.} = -11350°$ (*tr*), $[\Phi]_{240} = 0°$, $[\Phi]_{233} =$

+30960° (*pk*), $[\Phi]_{222}$ = +6800° (*tr*), $[\Phi]_{214}$ = +20640° (*pk*), $[\Phi]_{210}$ = 0°, $[\Phi]_{202}$ = −275200° (*tr*); CD. (*c* = 0.01 M, MeOH): $[\Theta]_{304}$ = 0, $[\Theta]_{288}$ = +15200, $[\Theta]_{280}$ = 0, $[\Theta]_{274}$ = −9000, $[\Theta]_{254}$ = −1800, $[\Theta]_{240}$ = −28000, $[\Theta]_{232}$ = 0, $[\Theta]_{225}$ = +15000 (infl.), $[\Theta]_{209}$ = +140000.

$C_{19}H_{23}NO_4$ (329.38) Calc. C 69.28 H 7.04 N 4.25% Found C 69.39 H 7.03 N 4.26%

(−)-(1S)-*6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline* (**3b**) *and its* (−)-*tartrate*. The 2-propanol mother liquors obtained from the crystallization of **4b** · DAG were combined, evaporated, the residue dissolved in water, rendered alkaline with 10% sodium hydroxide, extracted with ethyl acetate and the extract evaporated. The residue (24.9 g) and 10.3 g (0.075 mol) of (−)-tartaric acid were dissolved in warm ethanol and the solution stored at room temperature overnight. The resulting crystals (17.7 g) were filtered off and recrystallized from 200 ml of methanol to give 8.6 g (36% based on 0.05 mol present in **2b**) of **3b** · (−)-*tartrate*: m.p. 197–198°; $[\alpha]_D$ = −15.0° (H_2O).

$C_{19}H_{23}NO_4 \cdot C_4H_6O_6$ (479.49) Calc. C 57.61 H 6.10 N 2.92% Found ,, 57.79 ,, 6.40 ,, 2.85%

In the usual manner, 8.2 g (0.017 mol) of **3b** · (−)-tartrate was converted into the base which was crystallized from 2-propanol to give 4.2 g (76%) of **3b**: m.p. 115–116°; $[\alpha]_D$ = −34.0° ($CHCl_3$); in NMR. identical with **4b**; in ORD. and CD. mirror image of **4b**.

$C_{19}H_{23}NO_4$ (329.38) Calc. C 69.28 H 7.04 N 4.25% Found C 69.32 H 7.21 N 4.16%

(−)-(1S)-*6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline* (**3c**) *and its* (−)-*diacetone-2-keto-*L-*gulonate* (**3c** · DAG). A mixture of 35.9 g (0.1 mol) of **2c** and 29.2 g (0.1 mol) of (−)-diacetone-2-keto-L-gulonic acid hydrate was dissolved in 400 ml of warm ethanol and stored at room temperature overnight. The crystals formed were filtered off (the filtrate was used for the preparation of **4c**) and recrystallized from 300 ml of ethanol to give 25 g (79% based on 0.05 mol) of **3c** · DAG: m.p. 210–211°; $[\alpha]_D$ = −21.7° (MeOH).

$C_{20}H_{25}NO_5 \cdot C_{12}H_{18}O_7$ (633.70) Calc. C 60.65 H 6.84 N 2.21% Found ,, 60.75 ,, 7.08 ,, 2.18%

After addition of 75 ml of 10% sodium hydroxide to a solution of 24 g (0.038 mol) of **3c** · DAG in 100 ml of water the mixture was extracted with 200 ml of ethyl acetate. The extract was evaporated and the residue crystallized from 50 ml of ether to give 13.5 g (98%) of **3c**: m.p. 100–101°; $[\alpha]_D$ = −37.0° ($CHCl_3$); NMR.: δ 1.90 (*s*, 1 H, NH); 2.60–3.30 (*m*, 4 H, CH_2CH_2); 3.64, 3.77, 3.77, 3.81, 3.84 (*s*, 15 H, 5 OCH_3); 4.95 (*s*, 1 H, $H_{(1)}$); 6.28, 6.60 (*s*, 2 H, $H_{(5,8)}$); 6.46 (*s*, 2 H, $H_{(2',6')}$); ORD. (*c* = 0.358, MeOH): $[\Phi]_{700}$ = −73°, $[\Phi]_{589}$ = −108°, $[\Phi]_{295}$ = −5020° (*tr*), $[\Phi]_{286}$ = 0°, $[\Phi]_{279}$ = +6530° (*pk*), $[\Phi]_{262}$ = +1760° (*tr*), $[\Phi]_{250}$ = +5530° (*pk*), $[\Phi]_{244}$ = 0°, $[\Phi]_{228}$ = −63280° (*tr*); CD. (*c* = 0.0025 M, MeOH): $[\Theta]_{306}$ = 0, $[\Theta]_{286}$ = −7360, $[\Theta]_{278}$ = 0, $[\Theta]_{270}$ = +2610, $[\Theta]_{261}$ = +1610, $[\Theta]_{243}$ = +18080, $[\Theta]_{234}$ = 0, $[\Theta]_{216}$ = −110500, $[\Theta]_{210}$ = 0, $[\Theta]_{204}$ = +158700.

$C_{20}H_{25}NO_5$ (359.41) Calc. C 66.83 H 7.01 N 3.90% Found C 66.51 H 7.00 N 3.85%

(+)-(1R)-*6,7-Dimethoxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline* (**4c**). The ethanol mother liquor of crude **3c** · DAG was evaporated, the residue dissolved in water, rendered alkaline with 10% sodium hydroxide and extracted with ethyl acetate. The extract was evaporated and the residual solid crystallized from 100 ml of ether to give 6.7 g (37%) of **4c**: m.p. 98–99°; $[\alpha]_D$ = +36.7° ($CHCl_3$); in NMR. similar to **3c**; in ORD. and CD. mirror image of **3c**.

$C_{20}H_{25}NO_5$ (359.41) Calc. C 66.83 H 7.01 N 3.90% Found C 67.11 H 7.01 N 3.94%

3. Synthesis and Optical Purity of Cryptostylines I, II, and III. – Each of the nor-compounds **3a, b, c** and **4a, b, c** was converted by the following general procedure into the natural cryptostylines **5a, b, c** and their antipodes **6a, b, c**, respectively. A solution of 0.11 mol of the nor-precursor and 3 ml of 37% formaldehyde in 100 ml of methanol was hydrogenated at 3 atm. in the presence of 1 g of *Raney* nickel at room temperature until hydrogen uptake had ceased. The catalyst was filtered off, the filtrate evaporated and the residue distributed between a mixture of ethyl acetate and water. The organic extract was separated, filtered through a short column of aluminium oxide (activity grade II), the filtrate evaporated and the residue crystallized to afford the corresponding tertiary amine in 65–75% yield.

Each of the tertiary amines was treated with ethanolic hydrogen bromide and the resulting recrystallized hydrobromide was reconverted to the base whose specific rotation was identical with that of the original base.

(+)-(1S)-*6,7-Dimethoxy-2-methyl-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline* (**5a**) (*Natural Cryptostyline I*): m.p. 101–102° (from ether), $[\alpha]_D = +56.0°$ ($CHCl_3$) [Lit. [1]: m.p. 101–102°, $[\alpha]_D^{20} = +56°$ ($c = 2.7$, $CHCl_3$)]; identical in UV. and NMR. with the values reported [1]; ORD. ($c = 0.327$, MeOH): $[\Phi]_{700} = +65°$, $[\Phi]_{589} = +100°$, $[\Phi]_{319} = 0°$, $[\Phi]_{297} = -10150°$ (*tr*), $[\Phi]_{294} = 0°$, $[\Phi]_{284} = +21700°$ (*pk*), $[\Phi]_{266} = +1050°$ (*tr*), $[\Phi]_{247} = +9100°$ (*pk*), $[\Phi]_{240} = 0°$, $[\Phi]_{233} = -5950°$ (*sh*), $[\Phi]_{212} = -57490°$ (*tr*), $[\Phi]_{208} = 0°$, $[\Phi]_{200} = +152490°$ (*pk*); CD. ($c = 0.01$ M, MeOH): $[\Theta]_{302} = 0$, $[\Theta]_{292} = -19000$, $[\Theta]_{283} = 0$, $[\Theta]_{275} = +11500$, $[\Theta]_{255} = +1500$, $[\Theta]_{239} = +14500$, $[\Theta]_{230} = +7000$, $[\Theta]_{223} = +9000$, $[\Theta]_{217} = 0$, $[\Theta]_{206} = -112000$; **5a** was recovered unchanged (m.p. and $[\alpha]_D$) when heated for 18 h in ether or 1 N HCl or 1 N alcoholic NaOH[8]).

$C_{19}H_{21}NO_4$ (327.37) Calc. C 69.70 H 6.47 N 4.28% Found C 69.00 H 6.51 N 4.22%

5a-*hydrobromide*: m.p. 239–240° (ethanol-ether); $[\alpha]_D = +15.6°$ (MeOH); UV., λ_{max} (ε): 286 (7070), 238 nm (9700); NMR.: δ 2.87 (*d*, 3 H, J = 5 Hz, $\overset{+}{H}NMe$); 2.80–4.10 (*m*, 4 H, CH_2CH_2); 3.61, 3.85 (*s*, 6 H, 2 OCH_3); 5.33 (*d*, 1 H, J = 7 Hz, $H_{(1)}$); 5.95 (*s*, 2 H, OCH_2O); 6.12, 6.63 (*s*, 2 H, $H_{(5,8)}$); 6.75–7.10 (*m*, 3 H, $H_{(2',5',6')}$).

$C_{19}H_{21}NO_4 \cdot HBr$ (408.28) Calc. C 55.80 H 5.43 N 3.43% Found C 55.43 H 5.70 N 3.21%

(+)-(1S)-*6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline* (**5b**) (*Natural Cryptostyline II*): m.p. 117–118° (ether), $[\alpha]_D = +59.3°$ ($CHCl_3$) [Lit. [1]: m.p. 117–118°, $[\alpha]_D^{25} = +58°$ ($c = 0.28$, $CHCl_3$)]; identical in UV. and NMR. with the values reported [1]; ORD. ($c = 0.343$, MeOH): $[\Phi]_{700} = +97°$, $[\Phi]_{589} = +146°$, $[\Phi]_{307} = 0°$, $[\Phi]_{294} = -5750°$ (*tr*), $[\Phi]_{290} = 0°$, $[\Phi]_{280} = +21750°$ (*pk*), $[\Phi]_{263} = +5500°$ (*tr*), $[\Phi]_{243} = +21750°$ (*pk*), $[\Phi]_{237} = 0°$, $[\Phi]_{228} = -27500°$ (*sh*), $[\Phi]_{215} = -43750°$ (*tr*), $[\Phi]_{208} = 0°$, $[\Phi]_{202} = +112500°$ (*pk*); CD. ($c = 0.01$ M, MeOH): $[\Theta]_{300} = 0$, $[\Theta]_{287} = -19400$, $[\Theta]_{279} = 0$, $[\Theta]_{273} = +11000$, $[\Theta]_{254} = +2400$, $[\Theta]_{237} = +47000$, $[\Theta]_{225} = +18000$ (*sh*), $[\Theta]_{217} = 0$, $[\Theta]_{208} = -86000$.

$C_{20}H_{25}NO_4$ (343.41) Calc. C 69.95 H 7.33 N 4.08% Found C 69.84 H 7.45 N 3.96%

5b-*hydrobromide*: m.p. 230–231° (ethanol-ether); $[\alpha]_D = +21.5°$ (MeOH); UV., λ_{max} (ε): 281 (5730), 233 nm (15500) (infl.); NMR.: δ 2.71 (*b*, 3 H, $\overset{+}{N}CH_3$); 3.47, 3.75, 3.76, 3.76 (*s*, 12 H, 4 OCH_3); 5.58 (*m*, 1 H, $H_{(1)}$); 6.09, 6.85 (*s*, 2 H, $H_{(5,8)}$); 6.80–7.10 (*m*, 3 H, $H_{(2',5',6')}$).

$C_{20}H_{25}NO_4 \cdot HBr$ (424.32) Calc. C 56.61 H 6.18 N 3.30% Found C 56.77 H 6.03 N 3.49%

(+)-(1S)-*6,7-Dimethoxy-2-methyl-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline* (**5c**) (*Natural Cryptostyline III*): m.p. 122–123° (ether), $[\alpha]_D = +78.0°$ ($CHCl_3$), $[\alpha]_D = +70.1°$ ($c = 0.15$, $CHCl_3$) [Lit. [1]: m.p. 126–129°, $[\alpha]_D^{25} = +51°$ ($c = 0.15$, $CHCl_3$)[9]); identical in UV. and NMR. with the values reported [1]; ORD. ($c = 0.373$, MeOH): $[\Phi]_{700} = +144°$, $[\Phi]_{589} = +216°$, $[\Phi]_{297} = 0°$, $[\Phi]_{294} = -850°$ (*tr*), $[\Phi]_{292} = 0°$, $[\Phi]_{278} = +11750°$ (*pk*), $[\Phi]_{265} = +8000°$ (*tr*), $[\Phi]_{248} = +15500°$ (*pk*), $[\Phi]_{238} = 0°$, $[\Phi]_{232} = -8750°$ (*sh*), $[\Phi]_{220} = -20000°$ (*tr*), $[\Phi]_{215} = 0°$, $[\Phi]_{208} = +50000°$ (*pk*), $[\Phi]_{202} = 0°$, $[\Phi]_{198} = -110000°$ (*tr*); CD. ($c = 0.01$ M, MeOH): $[\Theta]_{300} = 0$, $[\Theta]_{285} = -7600$, $[\Theta]_{277} = 0$, $[\Theta]_{269} = +3800$, $[\Theta]_{259} = +2800$, $[\Theta]_{239} = +23000$, $[\Theta]_{225} = +11000$ (*sh*), $[\Theta]_{219} = 0$, $[\Theta]_{214} = -29000$, $[\Theta]_{211} = 0$, $[\Theta]_{202} = +125000$.

$C_{21}H_{27}NO_5$ (373.43) Calc. C 67.54 H 7.29 N 3.75% Found C 67.74 H 7.39 N 3.73%

5c-*hydrobromide*: m.p. 245–246° (ethanol); $[\alpha]_D = +21.7°$ (MeOH); UV., λ_{max} (ε): 281 (3970), 239 nm (14800) (infl.); NMR.: δ 2.72 (*s*, 3 H, $\overset{+}{N}CH_3$); 3.49, 3.69, 3.75, 3.75, 3.75 (*s*, 15 H, 5 OCH_3); 5.55 (*m*, 1 H, $H_{(1)}$); 6.10, 6.86 (*s*, 2 H, $H_{(5,8)}$); 6.78 (*s*, 2 H, $H_{(2',6')}$).

$C_{21}H_{27}NO_5 \cdot HBr$ (454.34) Calc. C 55.51 H 6.21 N 3.08% Found C 55.61 H 6.19 N 2.95%

(−)-(1R)-*6,7-Dimethoxy-2-methyl-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline* (**6a**) (*Unnatural Cryptostyline I*): m.p. 101–102° (ether); $[\alpha]_D = -56.9°$ ($CHCl_3$); identical in UV. and NMR. with **5a**; in ORD. and CD. mirror image of **5a**.

$C_{19}H_{21}NO_4$ (327.37) Calc. C 69.70 H 6.47 N 4.28% Found C 69.81 H 6.49 N 4.21%

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[8]) Natural cryptostyline I is reported to racemize in boiling ether [1].

[9]) A 2:1 mixture of **5c** and the corresponding racemate, m.p. 141–142° (Lit. [1]: m.p. 141–142°) recrystallized from ether: m.p. 125–128°, $[\alpha]_D = +48°$ ($CHCl_3$).

6a-*hydrobromide*: m.p. 239–240° (ethanol); $[\alpha]_D = -15.5°$ (MeOH); identical in UV. and NMR. with **5a**.

$C_{19}H_{21}NO_4 \cdot HBr$ (408.28) Calc. C 55.80 H 5.43 N 3.43% Found C 55.55 H 5.66 N 3.26%

(–)-(1R)-*6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline* (**6b**) (*Unnatural Cryptostyline II*): m.p. 117–118° (ether); $[\alpha]_D = -59.0°$ ($CHCl_3$); identical in UV. and NMR. with **5b**; in ORD. and CD. mirror image of **5b**.

$C_{20}H_{25}NO_4$ (343.41) Calc. C 69.95 H 7.33 N 4.08% Found C 70.18 H 7.56 N 4.04%

6b-*hydrobromide*: m.p. 230–231° (ethanol); $[\alpha]_D = -22.0°$ (MeOH); identical in UV. and NMR. with **5b**.

$C_{20}H_{25}NO_4 \cdot HBr$ (424.32) Calc. C 56.61 H 6.18 N 3.30% Found C 56.33 H 6.37 N 3.01%

(–)-(1R)-*6,7-Dimethoxy-2-methyl-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline* (**6c**) (*Unnatural Cryptostyline III*): m.p. 124–125° (ether); $[\alpha]_D = -77.5°$ ($CHCl_3$); identical in UV. and NMR. with **5c**; in ORD. and CD. mirror image of **5c**.

$C_{21}H_{27}NO_5$ (373.43) Calc. C 67.54 H 7.29 N 3.75% Found C 67.24 H 7.31 N 3.54%

6c-*hydrobromide*: m.p. 245–246° (ethanol-ether); $[\alpha]_D = -21.2°$ (MeOH); identical in UV. and NMR. with **5c**.

$C_{21}H_{27}NO_5 \cdot HBr$ (454.34) Calc. C 55.51 H 6.21 N 3.08% Found C 55.89 H 6.28 N 2.89%

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166. Etudes sur les composés organométalliques, XIII [1] Action d'organomagnésiens sur la benzalacétone

par **George Jon Dubsky** et **André Jacot-Guillarmod**
Institut de chimie de l'Université, Neuchâtel

(15 VI 71)

Summary. The reactions of benzalacetone with *n*-BuMgBr and PhMgBr have been compared with the corresponding reactions with the diorganomagnesium complexes of ether and pyridine. The results obtained by using different mole ratios of reactants and orders of addition show that the conjugated addition reaction is enhanced if a monomeric diorganomagnesium reagent is available; this condition can be realized either by adding a diorganomagnesium complex to the ketone or by complexing the diorganomagnesium with pyridine. Probable reaction mechanisms for normal and conjugated addition reactions are suggested.

Les cétones α,β-insaturées peuvent réagir avec des organomagnésiens par addition normale 1–2 ou par addition conjuguée 1–4, de manière à former respectivement un alcool α,β-insaturé ou une cétone saturée.