227. Preparation of a 2-Methylcyclodopa Derivative

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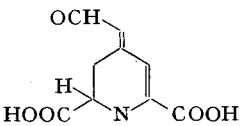
Zusammenfassung. Die Herstellung von O,O-Diacetyl-*S*-2-methylcyclodopa-methylester (**7**) durch Oxydation von *S*-2-Methyldopa-methylester (**4**) und anschliessende Reduktion und Acetylierung ist beschrieben. Im Gegensatz zu Cyclodopa (**2**) wird 2-Methylcyclodopa-methylester (**6**) am Stickstoff durch Acetanhydrid und Pyridin nicht acetyliert.

Betanidin, the aglucone of the violet pigment of the beet, consists of two moieties connected by an immonium bond: Betalamic acid (**1**) and cyclodopa (**2**) [1]. In connection with our work on the synthesis of compounds related to betanidin [2] we have



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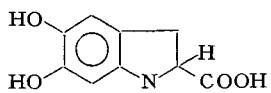

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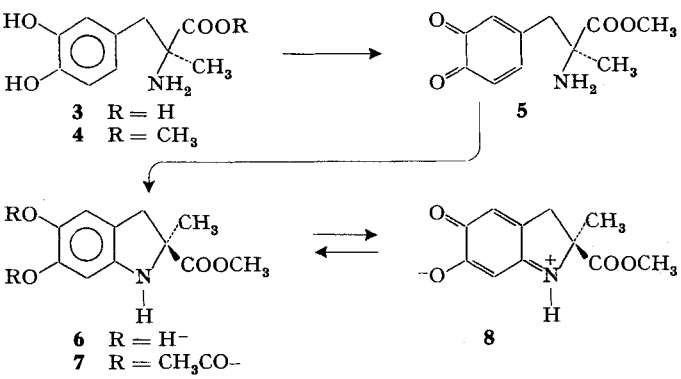
prepared a derivative of 2-methylcyclodopa. In view of the recent pharmacological interest in 3,4-dihydroxyphenylalanine (dopa) and its 2-methyl derivative (**3**) we describe our procedure now. The method is the same as used by *Wyler & Chiovini* [3] for the synthesis of a cyclodopa (**2**) derivative.



3 R = H
4 R = CH_3

5

6 R = H
7 R = CH_3CO–

8

S-2-Methyldopa-methyl ester (**4**, prepared from **3** by the method of *Brenner & Huber* [4]) was oxidized in a buffered solution (pH 8) with potassium hexacyanoferrate(III). The presumed intermediate **5** probably cyclized rapidly to *S*-2-methylcyclodopa methyl ester (**6**) which, in turn, was oxidized further by the hexacyanoferrate(III) as fast as produced to 2-*S*-dopachrome methyl ester (**8**). The latter cumu-

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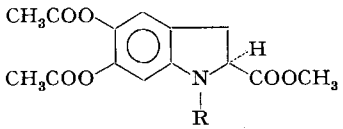
lated in the solution, but was reduced to **6** by the almost immediate addition of an excess of sodium dithionite. After acetylation with acetic anhydride and pyridine, O,O-diacetyl-*S*-2-methylcyclodopa methyl ester (**7**), m.p. 110°, was isolated. The spectroscopic properties confirm the indicated structure.

It is of interest that – in contrast to the behaviour of cyclodopa (**2**) itself – the nitrogen is not acetylated under these conditions. This effect is probably ascribable to a steric hindrance at the nitrogen produced by the additional methyl group at position 2 in 2-methylcyclodopa derivatives (for instance **6** and **7**).

The circular dichrogram (in methanol) of O,O-diacetyl-*S*-2-methylcyclodopa methyl ester (**7**) shows a positive major extremum (256 nm, $\Delta\varepsilon = +3.35$), which is enantiomeric to the major extremum (252 nm, $\Delta\varepsilon = -11{,}4$) of O,O,N-triacetyl-*S*-



9 R = CH_3CO
10 R = H

cyclodopa methyl ester (**9**). That this effect is not to be ascribed to the α-methyl group of **7**, but rather to the missing N-acetyl group, is shown by the CD.-curve[2]) of the recently synthesized [5] O,O-diacetyl-*S*-cyclodopa methyl ester (**10**), which also exhibits a positive major extremum (249 nm, $\Delta\varepsilon = +3.17$).

Pharmacological tests were performed with O,O-diacetyl-*S*-2-methylcyclodopa methyl ester (**7**) by Dr. *W. P. Burkard* of *F. Hoffmann-La Roche & Co., AG*, Basle. The preliminary results[3]) can be summarized as follows: After intraperitoneal or oral application of 0.1 to 1.0 mmole/kg of **7**, no effect on aromatic amino acid decarboxylase was observed in rat kidneys. Two intraperitoneal applications of 0.3 mmole/kg **7** left the content of noradrenaline and dopamine in rat brain and heart unchanged.

This work was supported by the *Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung*. We are also grateful to *F. Hoffmann-La Roche & Co., AG*, Basle, for a research grant.

Experimental. – The melting points are uncorrected. The UV. spectra were obtained with a *Beckman* model DK2, the CD. spectra with a *Jouan* Circular Dichrograph CD 185, the IR. spectra in a *Perkin-Elmer* model 21, and the NMR. spectra with a *Varian* HA-100 model spectrometer. The spectra are recorded as follows: *UV.* (solvent): max. wavelength (intensity) nm (ε); *CD.* (solvent, concentration): maxima, minima in nm ($\Delta\varepsilon$); *IR.* (solvent): wavelength (intensity symbol, *st*, *m*, *w*) μ; *NMR.* (solvent): δ-value in ppm/multiplicity (*J*-values in Hz) number of protons, pr. (assignment); δ (Hz). The following abbreviations are used in the description of the NMR.-spectra: *s* = singlet, *tr* = triplet, *m* = multiplet, *b* = broad. Tetramethylsilan was used as internal standard.

The elementary analyses and IR. spectra were carried out by *H. Frohofer* and his staff in the Microanalytical Laboratory of the Organic Chemistry Institute of the University of Zürich. The CD. spectra were kindly measured by Mr. *W. Hug*, Physical Chemistry Institute of the University of Zürich.

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[2]) We are grateful to *Wölcke, Kaiser, Koch & Scheer* [5] for having measured this circular dichrogram of **10** and for making the results available to us.

[3]) We are grateful to Dr. *W. P. Burkard* for the permission to mention these unpublished results here.

O,O-Diacetyl-S-2-methylcyclodopa Methyl Ester (**7**). – a) *Esterification of S-2-Methyldopa* (**3**). The methyl ester of *S*-2-methyldopa (**4**) was prepared using the procedure of *Brenner & Huber* [4]: Under magnetic stirring, 10 ml of thionyl chloride were added dropwise to 40 ml dry methanol at -10 to $-5°$. After addition of 2.0 g (9.6×10^{-3} moles) of *S*-2-methyldopa (**3**), the reaction mixture was stirred at room temperature for 2 hours and then under reflux for 1 hour. Evaporation of the reaction mixture in a rotary evaporator left a thick yellow syrup. This material (containing **4**) was used for the next step without further purification.

b) *Oxidative Cyclization of S-2-Methyldopa Methyl Ester* (**4**) *and Acetylation of the Product.* The above yellow syrup was dissolved in 600 ml of a *Sörensen* phosphate buffer pH 8 (0.5 g KH_2PO_4 and 22.6 g Na_2HPO_4 in 1 l of water). To this vigorously stirred solution, 16.3 g of potassium hexacyanoferrate (III) in 400 ml of the same buffer were added at once to give a dark red reaction mixture. After 3 to 5 seconds, a freshly prepared solution of sodium dithionite ($Na_2S_2O_4$) in 200 ml buffer solution was quickly poured into the mixture resulting in the formation of a yellow solution to which 20 ml of conc. HCl were added immediately. This solution was combined with a solution prepared from another 2.0 g of *S*-2-methyldopa under the reaction conditions described above.

The combined solutions were evaporated in a rotary evaporator to about 30 ml. Precipitated sulfur was removed by filtration over Celite and the filtrate concentrated to dryness. After thorough drying under high vacuum, the residue was taken up in 200 ml of acetic anhydride and treated with 200 ml of pyridine. The mixture was left overnight, then filtered by suction and the solids washed with CH_2Cl_2. The combined filtrates and washings were evaporated to about 50 ml. This residue was taken up in 400 ml 0.5N HCl and extracted with CH_2Cl_2. The organic extracts were washed twice with 50 ml of 5% $NaHCO_3$ then with water, and dried over $MgSO_4$, filtered, and concentrated, leaving 4.60 g of a light brown syrup which solidified in part on trituration with ether, giving 2.35 g of light tan crystalline product.

Evaporation of the mother liquor left 1.8 g of a brown syrup, which was shown by TLC. analysis (Polygram silicagel plates; CH_2Cl_2:CH_3OH = 19:1) to consist essentially of O,O-diacetyl-*S*-2-methylcyclodopa methyl ester (major spot: Rf 0.68). The other spots of minor intensity were: Rf = 0.78 (sulfur), Rf = 0.62 and Rf = 0.35 (unknown products). The syrup was chromatographed on a column of 100 g of silicagel (*Merck*, 0.05–0.5 mm), first using ~200 ml of CH_2Cl_2 and then 500 ml of CH_2Cl_2:CH_3OH (19:1), taking fractions of 50 ml. The first 4 fractions contained decreasing amounts of sulfur and the following 250 ml only traces of it. The next 100 ml of eluate provided 0.76 g of product. This material was combined with the previously obtained O,O-diacetyl-*S*-2-methylcyclodopa methyl ester (**7**); total yield: 3.11 g (53%). In order to remove traces of sulfur, 2,7 g of the above material was chromatographed over 120 g of silicagel by the procedure described above; 2.34 g of product (along with 105 mg of sulfur) were recovered. Recrystallization from 12 of mlisopropanol (at $-20°$ for several hours) gave 2.11 g of crystals, m.p. 108.5–109.5°. Repeated recrystallisation yielded analytically pure **7**, m.p. 109.5–110.5°. $[\alpha]_D^{23} = +0.35°$ (c = 0.86 in CH_3OH). UV. (CH_3OH): Max. 243 (9400), 301 (4070) nm (ε). IR. (CH_2Cl_2): 2.96 *w*; 3.43 *w*; 5.67 *s*; 6.15 *m*; 6.68 *s*; 6.95 *m*; 7.30 *s*; 7.50 *m*; 8.25 *s*; 8.42 *s*; 8.90 *m*; 9.20 *s*; 9.93 *m*; 10.19 *w*; 10.60 *w*; 10.90 *m*; 11.17 *m*; 11.50 *w*; 11.85 *w*; 12.16 *w*; μ. NMR. ($CDCl_3$): 6.82/*tr* (J = ~1), 1 pr. (H–C4); 6.40/*s*, 1 pr. (H–C7): 4.62/*b*, 1 pr. (H–N); 3.72/*s*, 3 pr. (CH_3O); 3.56/*bd* (J = 16.0), 1 pr. (probably Hβ–C3); 2.92/*d* × tr (J = 16.0 & J = ~1), 1 pr. (probably Hα–C3); 2.22/*s*, 6 pr. (2 × CH_3CO); 1.53/*s*, 3 pr. (CH_3–C2); δ (Hz). CD. (CH_3OH, conc. 0.21 mg/ml): Infl. 300 (+0.6); max. 257 (+3.35); min. 230 (−0.25); max. 212 (+2.40); end 200 (−1.2) nm ($\Delta\varepsilon$).

$C_{15}H_{17}NO_6$ (307.3) Calc. C 58.63 H 5.58 N 4.56% Found C 58.42 H 5.53 N 4.49%

CD.-Spectrum of O,O-Diacetyl-S-cyclodopa Methyl Ester (**10**)[2]: *CD.* (CH_3OH, conc. = 7.85 mg/ml): Min. 312 (−0.27); infl. ~298 (~0); max. 249 (+3.17); end 200 (−0.9) nm ($\Delta\varepsilon$).

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