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221. A Total Synthesis of the Alkaloid Rhoeadine

Preliminary communication[1])

by **W. Klötzer**[2]), **S. Teitel** and **A. Brossi**

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

(29. VII. 71)

Zusammenfassung. Die Umwandlung des Phtalidisochinolins (–)-Bicucullin (**1**) in das Benzazepinalkaloid (+)-Rhoeadin (**8**) und in sein unnatürliches Isomeres werden beschrieben.

Based on model experiments for the preparation of benzazepines from the phthalide alkaloids (–)-α-narcotine[1]) [1] and (–)-β-hydrastine[1]), the phthalide-isoquinoline (–)-bicuculline (**1**) has been converted by a new, straightforward synthesis into the benzazepine alkaloid (+)-rhoeadine (**8**)[3]) and its unnatural antipode. Since **1** was obtained from (–)-β-hydrastine[4]) which has been previously synthesized [3], the following transformations[5]) constitute the first total synthesis of natural rhoeadine[6]).

Reaction of (–)-bicuculline (**1**) [m.p. 193–194°, $[\alpha]_D^{33} = -128°$ ($c = 0.27$, $CHCl_3$); lit. [5]: m.p. 193–195°, $[\alpha]_D^{33} = -110°$ ($c = 0.27$, $CHCl_3$)] with phenyl chloroformate and di-isopropylethylamine, followed by dehydrohalogenation with a mixture of dimethyl sulfoxide and di-isopropylethylamine yielded the urethane **2** (> 90% yield).

[1]) Details will be published in Mh. Chem.

[2]) Visiting Professor, Institute of Organic and Pharmaceutical Chemistry, University of Innsbruck, Austria.

[3]) The formulas **6**, **7** and **8** show the absolute configurations as suggested by *Šantavý* for rhoeadine [2]. – *Added in proof:* The configurations given have in the meanwhile been verified by *X*-ray study of rhoeagenine methoiodide being published in Acta crist. (personal communication by *C. S. Huber,* Biochem. Lab., National Research Council, Ottawa 7, Canada).

[4]) Details will be published elsewhere.

[5]) All isolated compounds gave acceptable elemental analyses. Unless noted otherwise, the UV. spectra were measured in ethanol, the IR. spectra were determined in a KBr pellet and the NMR. spectra were obtained using $CDCl_3$ as solvent.

[6]) The synthesis of a (±)-rhoeadine precursor from a *spiro*-isoquinoline has been recently reported [4].

Data for **2**: m.p. 205–206°; UV., λ_{max}: 223 (24800), 309 (12700), 381 (22000) nm (ε); IR., ν_{max}: 1775, 1700 cm^{-1}; NMR.: δ 3.04 (*s*, 3, NCH_3); 3.46 (*m*, 4, NCH_2CH_2); 5.93, 6.14 (2*s*, 4, 2 OCH_2O); 6.68 (*s*, 1, vinyl proton); 6.65–7.75 (*m*, 9, aromatics).

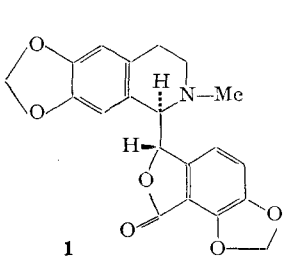
2 was treated with 2N sodium hydroxide in a nitrogen atmosphere to afford the dihydrobenzazepine sodium salt **3** [80% yield; dec. >300°; UV., $\lambda_{max}^{H_2O}$: 333 nm (ε = 17200)].

Acidification of an aqueous solution of **3** with acetic acid effected cyclization to the spirolactone **4** which was not isolated but dissolved in ethanol and readily oxidized by air to provide the keto-lactone **5** (62% yield).

Data for **5**: m.p. 195–197° (dec.); UV., λ_{max}: 215 (35700), 327 (11000) nm (ε); IR., ν_{max}: 1762, 1695 cm^{-1}; NMR.: δ 2.33 (*s*, 3, NCH_3); 3.24 (*m*, 4, CH_2CH_2); 5.96, 6.16 (2*s*, 4, 2 OCH_2O).

Reduction of **5** with lithium borohydride in tetrahydrofuran followed by acidification with acetic acid afforded, *via* the transient *cis*-hydroxy acid **6**, the *cis*-lactone (±)-oxyrhoeagenine [(±)-**7**] (75% yield).

Data for (±)-**7**: m.p. 241–243° (dec.); UV., λ_{max}: 223 (27400) (sh), 242 (12000) (infl.), 292 (5700), 327 (5300) nm (ε); IR., ν_{max}: 1725 cm^{-1}; NMR.: δ 2.11 (*s*, 3, NCH_3); 3.27, 5.19 (*d*'s, 2H, J = <1 Hz); 5.90, 6.11 (2*s*, 4, 2 OCH_2O); 6.70–6.90 (*q*, 2, aromatic); MS.: *m/e* 367 (M^+); identical, within experimental error, in UV. and IR. with data reported for oxyrhoeagenine [6].



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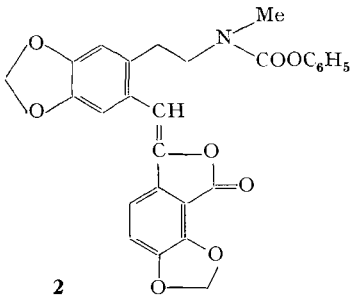

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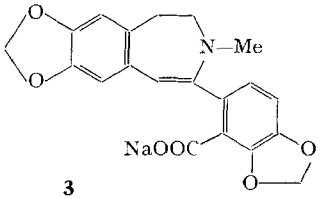

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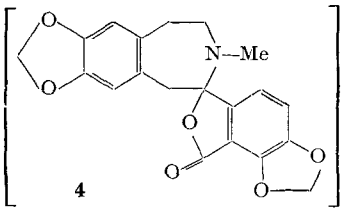

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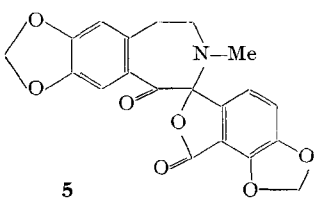

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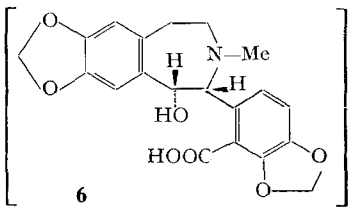

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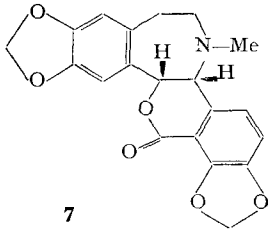
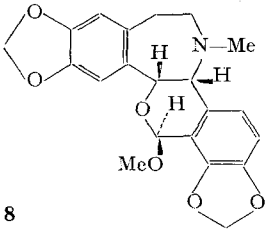


7



8

*) Not isolated in pure form.

Resolution of (±)-**7** with (+)-10-camphorsulfonic acid in methanol and neutralization of the precipitated diastereomeric salt, provided (–)-oxyrhoeagenine (mirror image of **7**) [80% of theory; m.p. 228–230°; $[\alpha]_D^{24} = -59.1°$ ($c = 0.55$, $CHCl_3$)]. Treatment of the mother liquors (as the free base) with (–)-10-camphorsulfonic acid[7]), followed by neutralization of the resulting diastereomeric salt, yielded (+)-oxyrhoeagenine (**7**)[3]) (80% of theory).

Data for **7**: m.p. 228–230°; $[\alpha]_D^{24} = +60°$ ($c = 0.5$, $CHCl_3$) [lit. [6]: m.p. 228–230°; $[\alpha]_D = +61°$ ($c = 0.55$, $CHCl_3$)].

Partial reduction of a pyridine solution of **7** at –70° with sodium bis-(2-methoxyethoxy)-aluminium hydride, followed by storage overnight at –20° and column purification, yielded a mixture of anomeric lactols which were etherified in methanol with trimethyl orthoformate catalyzed by mineral acid, to afford (+)-rhoeadine (**8**) (40% yield).

Data for **8**: m.p. 252° (dec.), $[\alpha]_D^{25} = +223°$ ($c = 1.1$, $CHCl_3$) [lit. [6]: m.p. 250–253°, $[\alpha]_D^{25} = +235°$ ($c = 1$, $CHCl_3$)]; UV., λ_{max}: 239 (9150), 290 (9180) nm (ε); NMR.: δ 2.28 (*s*, 3, NCH_3); 3.49 (*s*, 3, OCH_3); 5.72 (*s*, 1, $OCHOCH_3$); 5.90, 6.06 (2*s*, 4, $2\,OCH_2O$); 6.61, 6.71, 6.74 (3*s*, 4, aromatic); 3.55, 5.00 (*d*'s, 2H, $J = 2$ Hz); MS.: *m/e* 383 (M^+); identical with natural rhoeadine[8]) in m.p., TLC., UV. NMR. [6] and MS. [8].

In a similar manner, (–)-oxyrhoeagenine (mirror image of **7**) was converted into unnatural (–)-rhoeadine (mirror image of **8**) [40% yield; m.p. 252° (dec.); $[\alpha]_D^{25} = -222°$ ($c = 1$, $CHCl_3$); identical in UV., NMR., MS., and TLC. with **8**].

We thank Dr. *R. P. W. Scott* and the staff of our Physical Chemistry Department for the analytical and spectral data, and Mr. *J. Borgese* and Mrs. *J. Cheung* for technical assistance.

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[7]) Prepared from (–)-camphor according to the procedure of *Rewald* [7].
[8]) We are grateful to Professor *F. Šantavý* of Palacký University, Olomouc, Czechoslovakia, for providing us with a sample of natural rhoeadine.