# Total Synthesis of Rhodovibrin (OH-P481), Anhydrorhodovibrin (P481), and Rhodopin[1]

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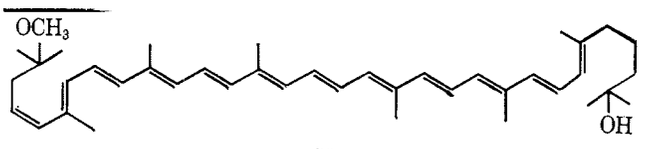
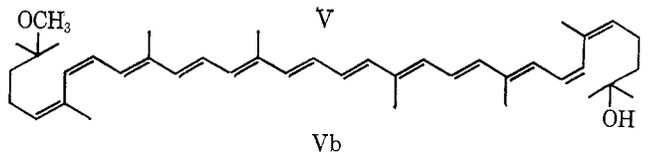
Rhodovibrin, anhydrorhodovibrin, and rhodopin were synthesized and shown to be identical with authentic samples of the natural products.

Goodwin[2] isolated two carotenoids from photosynthetic bacteria which were named P481 and OH-P481.[3] OH-P481 appeared to be identical with rhodovibrin described by Karrer, *et al.*[4-6] On the basis of the structural relationship existing between OH-P481 and P481, the name anhydrorhodovibrin was suggested for P481.[7,8]

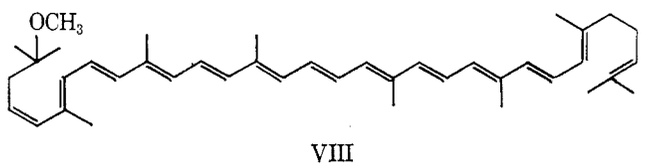
A study of the chemical constitution of these carotenoids led to the suggested structure V or Vb for rhodovibrin and VIII or VIIIb for anhydrorhodovibrin.[9]



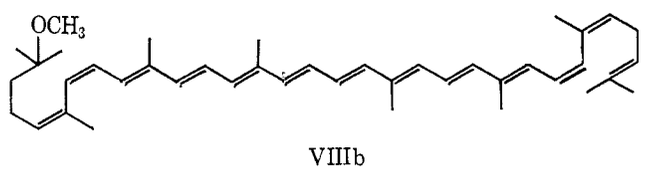
V



Vb



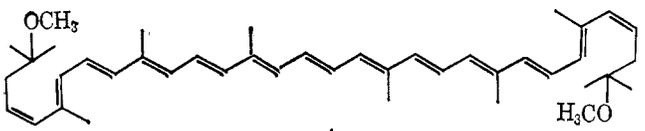
VIII



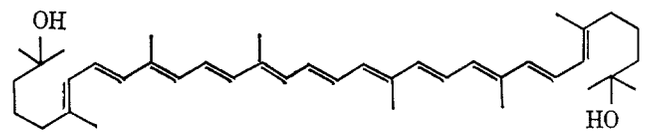
VIIIb

Structures V and VIII were favored for rhodovibrin and anhydrorhodovibrin by Jackman and Jensen[9] on biogenetic grounds. This preference was also supported by the isolation of 3,4-dehydrorhodopin, a third member of the P481 group.

In a previous communication,[10] the authors described the preparation of Wittig salts containing the hydroxyl or methoxyl groups which served as a basis for the synthesis of spirilloxanthin (A) and 1,1′-dihydroxy-1,2,1′,2′-tetrahydrolycopene (B).



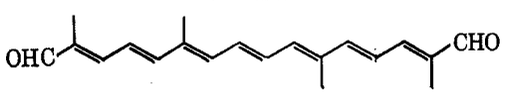
A



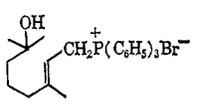
B

The synthetic A and B were demonstrated by Jensen[11] to be identical with the naturally occurring pigments. Continuation of this study has resulted in the synthesis of rhodovibrin (OH-P481), anhydrorhodovibrin (P481), and rhodopin, as outlined in

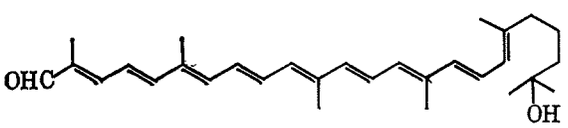
CHART I



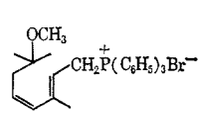
I



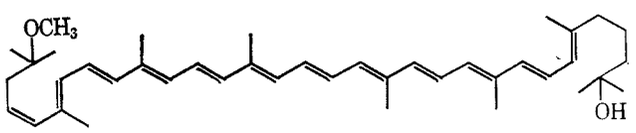
II



III



IV



V

(1) Presented at the IUPAC Symposium at Heidelberg, Germany, on May 21, 1964.

(2) T. W. Goodwin and D. G. Land, *Arch. Mikrobiol.*, **24**, 305 (1950).

(3) P481 and OH-P481 are the original names of the carotenoids used by Goodwin. The 481 corresponds to the wave length of the main adsorption maximum in petroleum ether.

(4) P. Karrer, U. Solmssen, and H. Koenig, *Helv. Chim. Acta*, **21**, 454 (1938).

(5) S. L. Jensen, *Acta Chem. Scand.*, **13**, 2143 (1959).

(6) M. S. Barber, L. M. Jackman, and B. C. L. Weedon, *Proc. Chem. Soc.*, 96 (1959).

(7) S. L. Jensen, *Acta Chem. Scand.*, **15**, 1182 (1961).

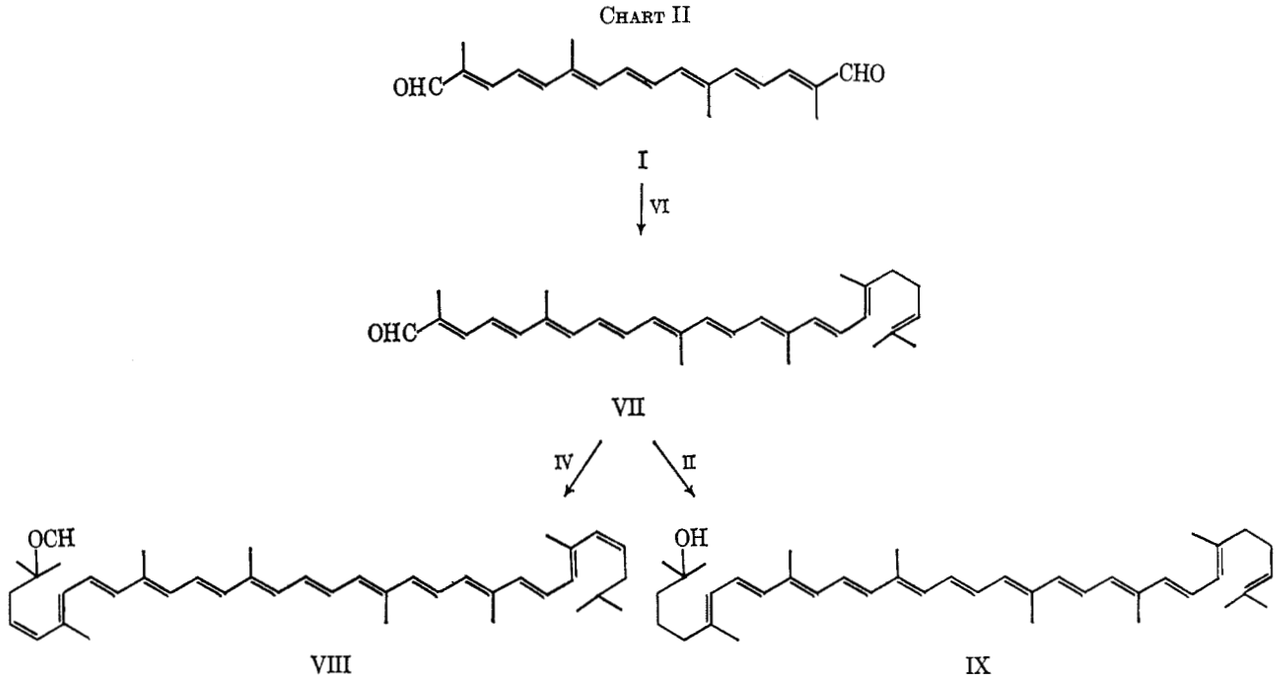
(8) S. Jensen, G. Cohen-Bazire, and R. Y. Stanier, *Nature*, **192**, 1168 (1961).

(9) L. M. Jackman and S. L. Jensen, *Acta Chem. Scand.*, **15**, 2058 (1961).

(10) J. D. Surmatis and A. Ofner, *J. Org. Chem.*, **28**, 2735 (1963).

(11) L. Ryvarden and S. L. Jensen, *Acta Chem. Scand.*, **18**, 643 (1964).

CHART II




Charts I and II. The synthetic compounds were identical with the natural products.[12]

1-Hydroxy-1,2-dihydroapo-3-lycopenal (III) was prepared by causing crocetindialdehyde[13] (I) to react with (7-hydroxy-3,7-dimethyl-2-octenyl)triphenylphosphonium bromide[10] (II) in benzene–methanol solution. After purification by chromatography on grade I alumina, followed by recrystallization from benzene, III was obtained in 42.3% yield as a dark red crystalline solid, m.p. 168°. The ultraviolet spectrum had maxima at 280, 449 ($E^{1\%}_{1\,cm}$ 1982), 474 ($E^{1\%}_{1\,cm}$ 2420), and 505 mμ ($E^{1\%}_{1\,cm}$ 1913) (in cyclohexane).

Condensation of III and (7-methoxy-3,7-dimethyl-2,4-octadien-1-yl)triphenylphosphonium bromide (IV)[10] in boiling methyl alcohol gave rhodovibrin (V) in 65% yield as a violet crystalline solid, m.p. 191°.

The *trans* isomer of the synthetic rhodovibrin could not be separated from *trans* rhodovibrin (isolated from *Thiocystis* sp. or *Rhodomicrobium vannielii*) on circular kieselguhr paper [$R_f$ 0.35 in 20% acetone–petroleum ether (b.p. 30–60°)]. The absorption spectrum in visible light, measured in petroleum ether, was identical with that of natural rhodovibrin: $\lambda_{max}$ at 358, 374, 455, 483, and 517 mμ. The infrared spectra measured in KBr gave satisfactory agreement for all bands.

After separate iodine catalysis in light[14,15] of the natural and the synthetic rhodovibrin, there was complete agreement in adsorptive properties as determined on cochromatography on circular kieselguhr paper.

For the synthesis of anhydrorhodovibrin (IX), crocetindialdehyde was condensed with (3,7-dimethyl-2,6-octadienyl)triphenylphosphonium bromide (VI)[10] to yield apo-3-lycopenal (VII) in 41.6% yield as purple plates, m.p. 141°. The absorption spectrum had maxima at 280, 449, 475 ($E^{1\%}_{1\,cm}$ 2839), and 505 mμ (in cyclohexane) (see Figure 1).

The Wittig condensation of VII with IV in a freshly prepared solution of sodium methoxide in methyl alcohol gave anhydrorhodovibrin as a violet crystalline solid, m.p. 182°.

The absorption spectra measured in visible light of the synthetic sample completely agreed with that of natural anhydrorhodovibrin with maxima at 358, 374, 455, 483, and 517 mμ. The *trans* isomer of the synthetic sample could not be separated from *trans*-anhydrorhodovibrin (isolated from *Rhodospirillum rubrum*) on circular kieselguhr paper ($R_f$ 0.40, 2% acetone–petroleum ether). Separate iodine catalysis of synthetic and natural anhydrorhodovibrin from *Thiocystis* sp. resulted in five separate zones. Cochromatography tests revealed identical $R_f$ values for corresponding stereoisomers.

When VII was condensed with II by the Wittig reaction, rhodopin[16] (IX) was obtained in 57% yield as a dark red crystalline solid, m.p. 182°. The absorption maxima were 296, 447, 474 ($E^{1\%}_{1\,cm}$ 2989), and 507 mμ (cyclohexane). The melting point of 173° agreed with that of natural rhodopin (172–174°). The infrared spectra measured in KBr showed good agreement between the natural and synthetic compounds for all bands. *trans* synthetic rhodopin could not be separated from the natural *trans* rhodopin on circular kieselguhr paper ($R_f$ 0.38 in 5% acetone–petroleum ether).

## Experimental Section[17]

**1-Hydroxy-1,2-dihydroapo-3-lycopenal (III).**—To a boiling solution of crocetindialdehyde[13] (90 g.) in benzene (2.5 l.), (7-hydroxy-3,7-dimethyl-2-octenyl)triphenylphosphonium bromide

(12) S. L. Jensen, Institute of Organic Chemistry, Norges Tekniske Høgskole, Trondheim, Norway, compared our synthetic compounds with authentic samples of the natural products.

(13) (a) H. H. Inhoffen and G. Respé, *Ann.*, **592**, 211 (1955); (b) O. Isler, H. Gutmann, H. Lindlar, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **54**, 463 (1956).

(14) L. Zeckmeister, *et al.*, *Arch. Biochem.*, **5**, 243 (1944).

(15) A. Jensen and S. L. Jensen, *Acta Chem. Scand.*, **13**, 1863 (1959).

(16) Upon reporting of the synthesis of rhodopin by the author at the IUPAC Symposium, May 1964, it was learned by private communication that Weedon had completed a synthesis for rhodopin. This has since been published by R. Bonnett, A. A. Spark, and B. C. L. Weedon, *ibid.*, **18**, 1739 (1964).

(17) The boiling and melting points are uncorrected. The melting points were determined in vacuum capillaries.

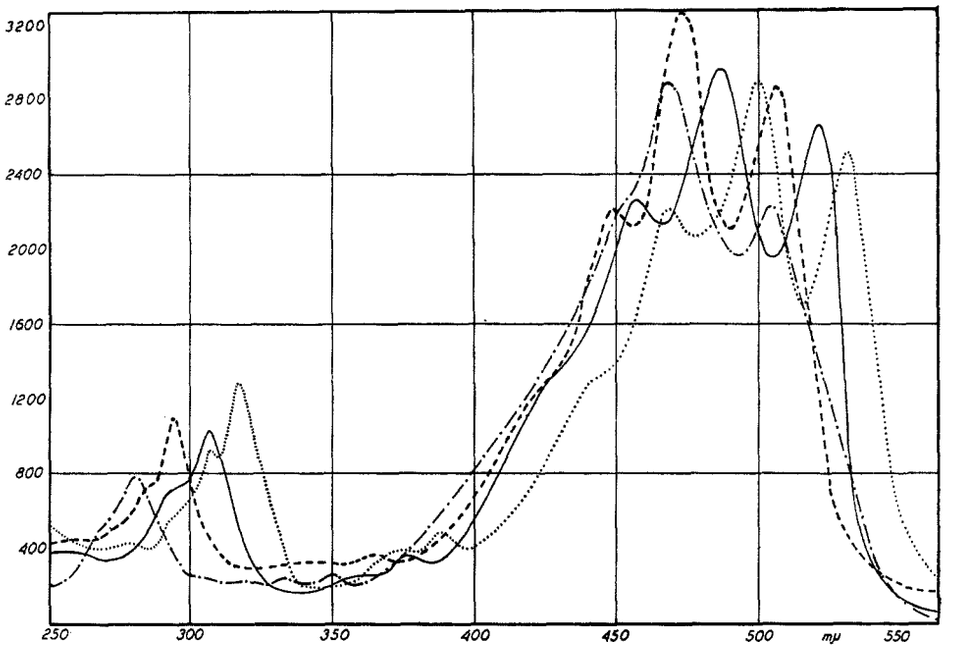



Figure 1.—The ultraviolet spectra in cyclohexane of rhodopin, – – – –; anhydrorhodovibrin, ———, spirilloxanthin, • • • •; and apo-3-lycopenal, — · —.

(II)[10] (100 g.) in methyl alcohol (400 ml.) was added dropwise simultaneously with a solution of sodium methoxide (from 10 g. of sodium) in methyl alcohol (400 ml.). The addition required 2 hr. Part of the benzene (1.5 l.) was distilled and replaced by an equal volume of methyl alcohol. Stirring was continued for 4 hr. longer under an atmosphere of nitrogen. The reaction mixture was stirred into ice–water (4 l.) and ether (2 l.) and filtered. The ether layer was separated, washed with water, and dried over Drierite. After distillation of the solvent, the residue (92.1 g.) was crystallized from ether–petroleum ether to yield 64 g. of crude III, m.p. 130–134°.

The resulting crude 1-hydroxy-1,2-dihydroapo-3-lycopenal (III) was chromatographed on grade I alumina (4 kg.). The column was developed with ether–benzene, the benzene content being finally increased to 95%. By this time, most of the remaining crocetindialdehyde had been removed as indicated by t.l.c. The contents of the column were pushed out and the portion containing III was extracted with methylene chloride. On removal of the solvent and recrystallization of the residue from benzene, there resulted 37 g. of III (42.3% based on II), m.p. 167–168°. The ultraviolet spectrum had maxima at 280, 449 ($E^{1\%}_{1\,cm}$ 1982), 474 ($E^{1\%}_{1\,cm}$ 2420), and 505 mμ ($E^{1\%}_{1\,cm}$ 1913)(in cyclohexane).

*Anal.* Calcd. for $C_{30}H_{42}O_2$: C, 82.90; H, 9.74. Found: C, 82.67; H, 9.90.

**Rhodovibrin (OH-P481) (V).**—To a freshly prepared 0.12 *M* solution of sodium methoxide in methyl alcohol (1 l.), the Wittig salt IV (28 g.) was added, and the solution was stirred for 5 min. 1-Hydroxy-1,2-dihydroapo-3-lycopenal (III) (4.0 g.) was added dropwise, and the solution was stirred at reflux temperature for 4 hr. After cooling overnight in a refrigerator, the product, which was obtained as a violet crystalline solid, was filtered and washed with methyl alcohol. After repeated recrystallizations from methylene chloride, an analytical sample of rhodovibrin (V) was obtained: 2.5 g. (46.5%), m.p. 191° in a vacuum capillary.

*Anal.* Calcd. for $C_{41}H_{60}O_2$: C, 84.19; H, 10.34; methoxyl, 5.31. Found: C, 84.60; H, 10.06; methoxyl, 5.31.

**Apo-3-lycopenal (VII).**—To a solution of crocetindialdehyde (I) (15 g.) in benzene (500 ml.), (3,7-dimethyl-2,6-octadienyl)-triphenylphosphonium bromide (VI) (12 g.) dissolved in methyl alcohol (75 ml.) was added simultaneously with a solution of sodium methoxide (from 0.6 g. of sodium) in methyl alcohol (75 ml.). The addition was made in 1 hr. at 30–35°. The solution was heated to reflux and stirred under an atmosphere of nitrogen for 4 hr. The product was washed with water and concentrated under vacuum. The residue (28 g.) was chromatographed on grade II alumina with benzene. On elution with benzene, the first band consisted of lycopene. This was followed by apo-3-lycopenal (VII) and finally by a third band of unreacted crocetindialdehyde (I). Evaporation of the solution from the second band, followed by recrystallization from benzene–methanol, resulted in 4.3 g. (41.6%) of apo-3-lycopenal (VII) as purple plates, m.p. 141°. The ultraviolet spectrum had maxima at 280, 475, ($E^{1\%}_{1\,cm}$ 2839), and 505 mμ (in cyclohexane).

*Anal.* Calcd. for $C_{30}H_{40}O$: C, 86.48; H, 9.67. Found: C, 86.32; H, 9.61.

**Anhydrorhodovibrin (P481) (VIII).**—The Wittig salt IV (28 g.) was caused to react with apo-3-lycopenal (VII) (4.2 g.) in a 0.12 *M* solution of sodium methoxide in methyl alcohol (1 l.) by the procedure described for the preparation of V. Anhydrorhodovibrin was obtained as a violet crystalline solid, 2.8 g. (49.4%), m.p. 182° after recrystallization from benzene.

*Anal.* Calcd. for $C_{41}H_{58}O$: C, 86.86; H, 10.31; methoxyl, 5.46. Found: C, 86.91; H, 10.08; methoxyl, 5.38.

**Rhodopin (IX).**—To a 0.1 *M* solution of freshly prepared sodium methoxide in methyl alcohol (250 ml.) there was added, with stirring under an atmosphere of nitrogen, 14 g. of the phosphonium salt II. Apo-3-lycopenal (VII) (2 g.) was added as a solid, and the reaction was stirred and heated at reflux for 4 hr. It was cooled overnight in a refrigerator, and the product, which was obtained as a bright red crystalline solid, was filtered and washed with additional methyl alcohol. After recrystallization from benzene–petroleum ether, there resulted 1.5 g. (57%) of rhodopin (IX), m.p. 182° (in a vacuum capillary).

*Anal.* Calcd. for $C_{40}H_{58}O$: C, 86.58; H, 10.54. Found: C, 86.41; H, 10.32.

**Acknowledgment.**—We wish to thank Dr. A. Steyermark and his staff for the microanalyses, Dr. F. Forrester and Mr. J. Volpe for the ultraviolet spectra, and Dr. S. Liaaen Jensen for comparison of the synthetic with samples of the natural compounds.