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Syntheses and Activities of Bioquinone Substances. I. Total Syntheses of Rhodoquinones

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The total syntheses of naturally occurring rhodoquinone-9 (I, $n=9$) and related compounds are described. The key intermediate, 2-halogeno-3-methoxy-6-methyl-1,4-benzoquinone (VI), was easily obtained by 5 steps starting from *p*-cresol.

i) Reduction of VI and condensation of the resulting hydroquinone (IX) with solanesol in the presence of BF_3·ether gave the nonaprenylated hydroquinone, which, on oxidation with Ag_2O, was transformed to 2-halogeno-3-methoxy-5-nonaprenyl-6-methyl-1,4-benzoquinone (X). Treatment of X with NaN_3 followed by reduction gave the azido hydroquinone from which rhodoquinone-9 (I, $n=9$) was prepared through pyrolysis. ii) Reaction of VI with NaN_3 followed by reduction gave the azido hydroquinone which was converted to rhodoquinone-0 (I, $n=0$) by pyrolysis. iii) An attempt to obtain (I, $n=0$) by direct conversion of the Br atom of VI to amino group failed, but 2-bromo-3-amino-6-methyl-1,4-benzoquinone (VII) and the cyclohexenedione compound (VIII) were obtained.

In 1962, Glover and Threlfall[2)] isolated a compound from *Rhodospirillum rubrum* and termed this substance rhodoquinone. A little later, Folkers and coworkers[3)] reported that rhodoquinone should be related to the aminobenzoquinone structure by the spectral evidence and further established unambiguously its structure to be 2-amino-3-methoxy-5-decaprenyl-6-methyl-1,4-benzoquinone (I, $n=10$) by the synthesis which was performed by ammonolysis of CoQ-10 (II, $n=10$),[4)] applying preparative thin-layer chromatography (TLC) together with multiple development technique to separate the desired product from the 2-methoxy-3-amino isomer (isorhodoquinone) which formed concurrently in much larger amount than the desired isomer. The alternative synthetic method was also reported by Folkers, *et al.*[5)] which consisted in amination of 3-methoxy-5-decaprenyl-6-methyl-1,4-benzoquinone prepared by the following sequence: condensation of 3-methoxy-6-methyl-1,4-hydroquinone with decaprenyl alcohol followed by oxidation of the intermediate hydroquinone to desired 3-methoxy-5-decaprenyl-6-methyl-1,4-benzoquinone which was separated from the reaction mixture contaminated mainly with the corresponding 2-decaprenylated and 2,5-didecaprenylated products. In this case, also, preparative TLC seemed to be an indispensable means of isolation and purification of the products.

Rhodoquinone-9 (I, $n=9$) was first isolated from *Euglena gracilis*[6)] and recently from *Ascaris lumbricoides* var. *suis* by one of us (Ozawa), Natori, and coworkers.[7–9)] In the latter work, the structural assignment was carried out by the syntheses which were succeeded by

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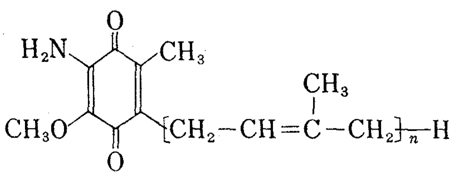
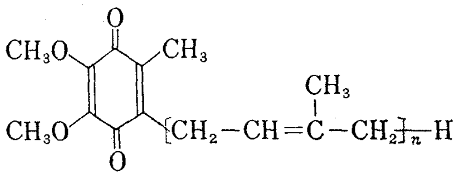
1) Location: *a) 34-1, Takata 3-Chome, Toshimaku, Tokyo; b) Aobayama, Sendai.*
2) J. Glover and D.R. Threlfall, *Biochem. J.*, **85**, 14 (1962).
3) H.W. Moore and K. Folkers, *J. Am. Chem. Soc.*, **87**, 1409 (1965).
4) H.W. Moore and K. Folkers, *J. Am. Chem. Soc.*, **88**, 567 (1966).
5) G.D. Daves, Jr., J.J. Wilczynski, P. Friis, and K. Folkers, *J. Am. Chem. Soc.*, **90**, 5587 (1968).
6) R. Powls and F.W. Hemming, *Phytochemistry*, **5**, 1235 (1966).
7) M. Sato and H. Ozawa, *J. Biochemistry*, **65**, 861 (1969).
8) H. Ozawa, M. Sato, S. Natori, and H. Ogawa, *Experientia*, **25**, 484 (1969).
9) H. Ogawa, S. Natori, M. Sato, and H. Ozawa, *Tetrahedron Letters*, **1969**, 1969.



I



II

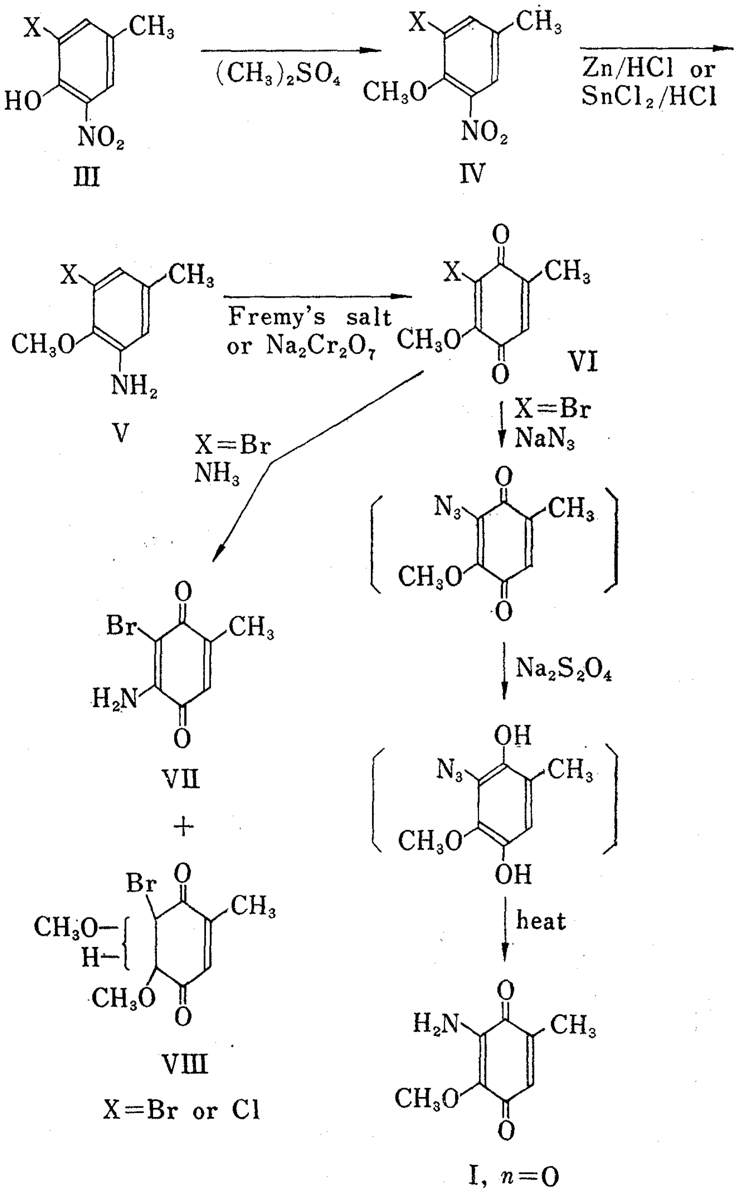


Chart 1

ammonolysis of CoQ-9 (II, $n=9$) and also by amination of 3-methoxy-5-nonaprenyl-6-methyl-1,4-benzoquinone isolated from *Pseudomonas ovalis*, respectively.

Rhodoquinone (I) is a relative of CoQ (II) which does play an important role in the electron transport system of living organism and is of biological interest. In view of the above situation, a novel synthesis of rhodoquinone (I) was undertaken by us. The synthetic route to rhodoquinone-O (I, $n=0$) was shown in Chart 1.

3-Halogeno-4-hydroxy-5-nitrotoluene (III, X=Br or Cl), prepared from p-cresol through halogenation and subsequent nitration,[10] was methylated with $(CH_3)_2SO_4$ and Na_2CO_3 in refluxing toluene, thereby 3-bromo-4-methoxy-5-nitrotoluene (IV, X=Br) and 3-chloro-4-methoxy-5-nitrotoluene (IV, X=Cl) were obtained in the yields of 73 and 89%, respectively. Subsequently, reduction of IV, (X=Br or Cl) with zinc dust and HCl or $SnCl_2$ and HCl was effectively made, and 3-bromo-4-methoxy-5-aminotoluene (V, X=Br) and 3-chloro-4-methoxy-5-aminotoluene (V, X=Cl) were obtained in 73 and 78% yields, respectively. The compound (V, X=Br) was oxidized with Fremy's salt[11] in an aqueous KH_2PO_4 solution at room temperature or with $Na_2Cr_2O_7$ and H_2SO_4 in aqueous acetone. After purification using silica gel column chromatography[12] and subsequent recrystallization, 2-bromo-3-methoxy-6-methyl-1,4-benzoquinone (VI, X=Br) melting at 62—63° was obtained, the yield of which attained 37% by the former method, while the latter resulted in 20% yield. IR[13] $\nu_{\max}^{\text{Nujol}}$ cm^{-1}:

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[10] T. Zincke, *Ann.*, **328**, 277 (1903).
[11] W. Moser and R.A. Howie, *J. Chem. Soc.*, (*A*), **1968**, 3039.
[12] Silica gel "Wakogel C-200" (Wakojunyaku Co., Ltd.) was used.
[13] Infrared (IR) spectra were recorded on a Nihonbunko DS 301.

1670 and 1653 (benzoquinone). NMR[14] τ: 3.62 (1H, quartet, ring H), 5.88 (3H, singlet, OCH_3), 7.93 (3H, doublet, CH_3). 2-Chloro-3-methoxy-6-methyl-1,4-benzoquinone (VI, X=Cl) melting at 58.5—59.3° was obtained in the yield of 30% in an analogous manner starting with the compound (V, X=Cl). IR ν_{max}^{Nujol} cm^{-1}: 1670 (benzoquinone).

2-Amino-3-methoxy-6-methyl-1,4-benzoquinone (rhodoquinone-0) (I, $n=0$) could be successfully synthesized in 25% yield from VI (X=Br) by the following reaction sequence. The reaction of VI (X=Br) with NaN_3 in 80% MeOH at room temperature provided the azide compound, which, without isolation, was reduced with $Na_2S_2O_4$ to the corresponding azidohydroquinone and, subsequently, the crude product was heated in 1,1,2-trichloroethane or $CHCl_3$ under reflux. The resulting product was submitted to silica gel column chromatography and finally purified by recrystallization from *n*-hexane to afford dark violet needles of I ($n=0$) melting at 91° (lit.[15] mp 91°). IR ν_{max}^{Nujol} cm^{-1}: 3420 and 3300 (NH_2), 1672 and 1645 (benzoquinone), 1600 (NH). NMR τ: 3.70 (1H, quartet, ring H), 5.3 (2H, broad, NH_2), 6.10 (3H, singlet, OCH_3), 8.02 (3H, doublet, CH_3).

Another run starting from the compound (VI, X=Cl) under the similar reaction conditon produced only an intractable mixture contaminated with large amount of by–product from which the isolation of I, ($n=0$) was unsuccessful.

On the other hand, an attempt to obtain I, ($n=0$) by direct conversion of the bromine atom of VI (X=Br) to amino group with NH_3 failed, however, the following two substances were obtained. To the solution of VI (X=Br) in ether–MeOH was introduced NH_3 gas under cooling and the reaction product was purified by silica gel column chromatography and subsequent recrystallization from petroleum ether–ether, thereby reddish violet needles of 2-bromo-3-amino-6-methyl-1,4-benzoquinone (VII) melting at 152—153.5° was obtained. The presence of Br was clearly detected by Beilstein's method. IR ν_{max}^{Nujol} cm^{-1}: 3420 and 3300 (NH_2), 1638 and 1645 (benzoquinone), 1580 (NH). NMR τ: 3.51 (1H, quartet, ring H), 4.6 (2H, broad, NH_2), 7.90 (3H, doublet, CH_3) (Fig. 1 and 2).

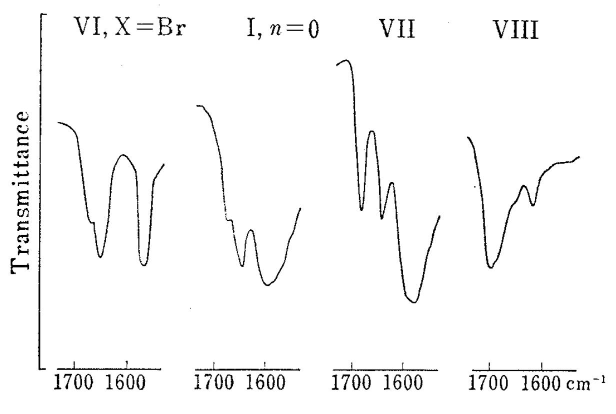

Fig. 1. IR Spectra (Nujol) in 1700—1600 cm^{-1} Region of VI (X=Br), I ($n=0$), VII and VIII

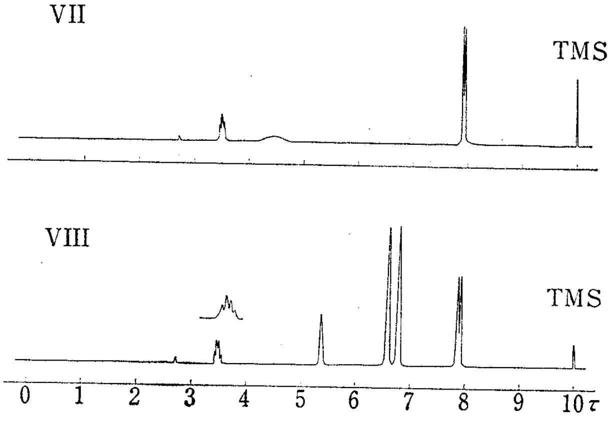

Fig. 2. NMR Spectra of VII and VIII in $CDCl_3$ (60 Mc)

The formation of VII should be reasonably interpreted as the result of nucleophilic attack of NH_3 on C-3 of VI (X=Br). Another crystal was isolated from the concentrate of the mother liquor and purified by recrystallization from petroleum ether to afford pale yellow prisms melting at 80—81°. Its infrared (IR) spectrum showed no absorption band due to OH group, while absorptions at 2810 and 1700 cm^{-1} were observed. The former should be ascribable

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[14] Nuclear magnetic resonance (NMR) spectra were obtained using a Hitachi Perkin–Elmer R-20 and samples were dissolved in $CDCl_3$ containing tetramethylsilane as an internal standard.

[15] K. Koshi and M. Shimizu, *Chem. Pharm. Bull* (Tokyo), **16**, 2343 (1968).

to the ν_{C-H} of OCH_3[16] and the latter to the $\nu_{C=O}$ of carbonyl function, which could not be assigned to the benzoquinone carbonyl, since benzoquinone derivatives exhibit ordinarily the band[17] near by 1670 cm^{-1} (Fig. 1), thus indicating that the substance was not possessed of the benzoquinone structure. It was further supported by the ultraviolet (UV) spectrum,[18] since this compound had no prominent absorption maximum in the region of 210—340 mμ in contrast to the spectra of I (n=1), VI and II (n=0), those exhibited, without exception, the characteristic absorption maxima due to the benzoquinone structure in this region (Fig. 3).

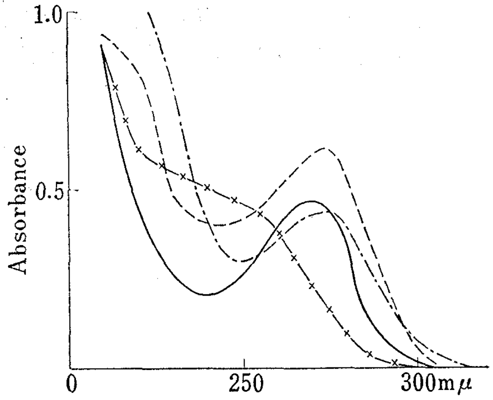
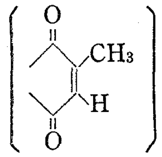


Fig. 3. Ultraviolet Absorption Spectra (in EtOH)

——: VI, X=Br, ------: VII,
—·—: I (n=0), —×—: VIII

As shown in Fig. 2, its NMR spectrum showed absorption peaks at τ 3.45 (1H, quartet), 5.35 (1H, singlet), 6.60 (3H, singlet), 6.80 (3H, singlet) and 7.93 (3H, doublet). Signals at τ 6.60 and 6.80 could be assigned to two methoxy groups and it was observed that the resonance at τ 7.93 was coupled with a one proton at 3.45, suggesting a long range coupling between CH_3 and H in the following moiety:  Furthermore, the presence of Br was proved by Beilstein's method. From the above evidence and the data of elemental analysis and molecular weight determination,[19] this substance should

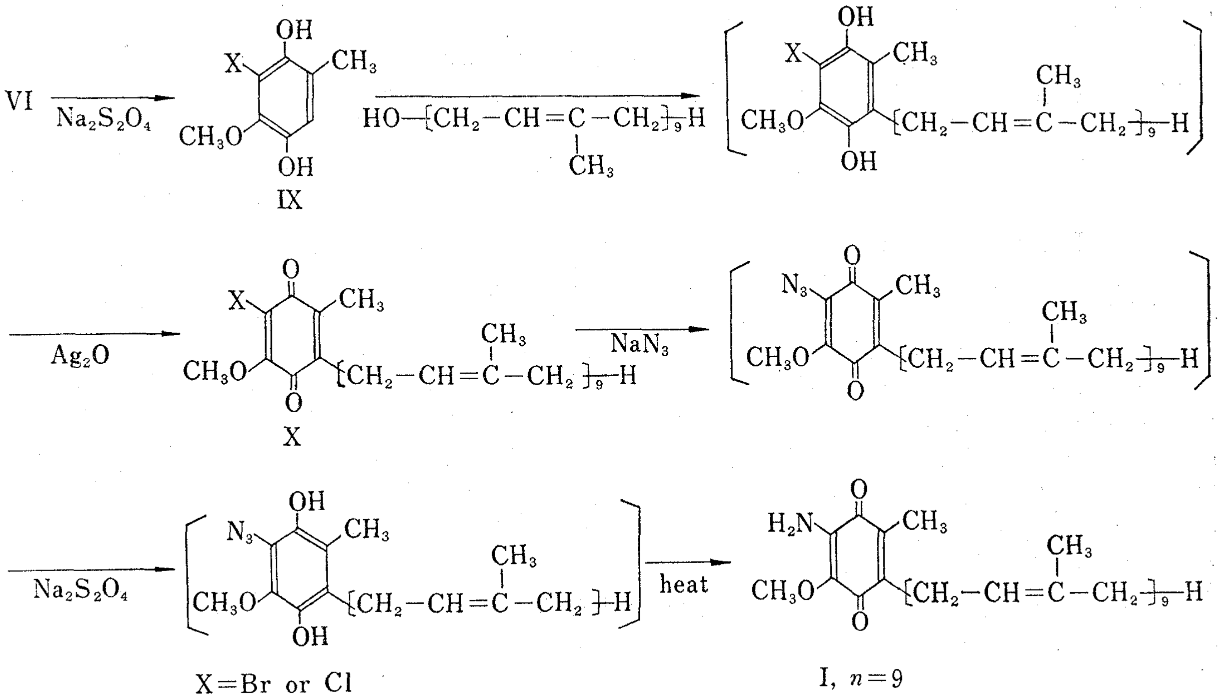


Chart 2

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[16] K. Nakanishi, "IR Absorption Spectroscopy -Practical-," 4th Ed., Nankodo, Tokyo, 1963, p. 42.

[17] L.J. Bellamy, "The Infrared Spectra of Complex Molecules," John Willy and Sons, Inc., New York, N. Y., 1964, p. 150.

[18] UV spectra were recorded on a Hitachi EPS-2U using EtOH as a solvent.

[19] Molecular weight determination was carried out with a Hitachi Perkin-Elmer 115 using EtOH as a solvent.

be regarded as the cyclohexenedione derivative (VIII), formed by addition of the CH_3OH molecule to the double bond of (VI, X=Br), although the strict structural confirmation still remains to be resolved.

The synthetic scheme of rhodoquinone-9 (I, $n=9$) was presented in Chart 2.

When 2-bromo-3-methoxy-6-methyl-1,4-hydroquinone (IX, X=Br), prepared almost quantitatively by the reduction of VI (X=Br) using $Na_2S_2O_4$, was condensed with nonaprenyl alcohol (solanesol) in dioxane using $BF_3\cdot$ether as a condensing agent, followed by oxidation of the intermediate hydroquinone with Ag_2O giving the product which was chromatographed on an aluminum oxide[20] column and further on a silica gel column, thereby a yellow solid was obtained. Recrystallization from ether–MeOH gave yellow grains of 2-bromo-3-methoxy-5-nonaprenyl-6-methyl-1,4-benzoquinone (X, X=Br) melting at 37—39° in 10% yield. IR ν_{max}^{Smear} cm^{-1}: 1633 (benzoquinone). NMR τ: 4.85 (9H, multiplet, $-CH{=}\overset{|}{C}-$), 5.83 (3H, singlet, OCH_3), 6.8 (2H, doublet, ring-CH_2–), 7.8—8.1 (35H, side chain $-CH_2-$ and ring-CH_3), 8.26 (3H, *trans* ring-$CH_2CH{=}\overset{|}{C}-C\underline{H}_3$), 8.34 (3H, *cis* terminal $-CH{=}\overset{|}{C}-C\underline{H}_3$), 8.40 (24H, *trans* $-CH{=}\overset{|}{C}-C\underline{H}_3$) (Fig. 4).

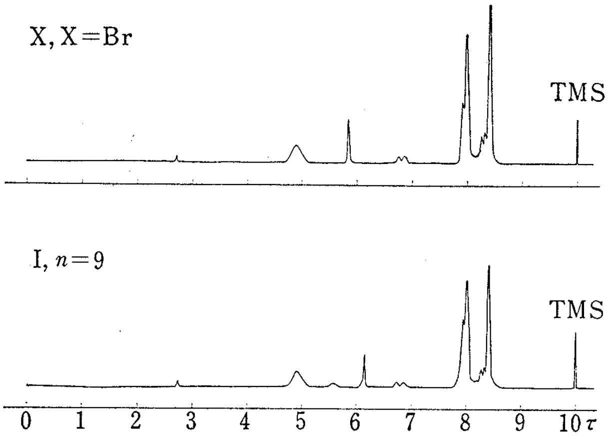

Fig. 4. NMR Spectra of X, (X=Br) and I ($n=9$) in $CDCl_3$ (60 Mc)

Since both the signal's intensities at τ 8.26 and 8.34 were almost equal, it should be concluded that the isoprenyl side chain of X (X=Br) was of all *trans* configuration.[21]

Similarly, reaction of the compound (IX, X=Cl) with nonaprenyl alcohol followed by oxidation with Ag_2O and subsequent chromatographic separations yielded 2-chloro-3-methoxy-5-nonaprenyl-6-methyl-1,4-benzoquinone (X, X=Cl) as a semisolid (15% yield), IR ν_{max}^{Smear} cm^{-1}: 1665 and 1600 (benzoquinone), which was used in the next step without further purification.

Finally, the compound (X, X=Br or Cl) was reacted with NaN_3 in ether–MeOH or ether–aqueous MeOH under reflux, thereby the corresponding azido compound was formed which, without isolation, was subjected to reduction with $Na_2S_2O_4$. The crude hydroquinone, thus obtained, was refluxed in 1,1,2-trichloroethane or $CHCl_3$ under nitrogen and the crude product was purified by silica gel column chromatography and subsequent recrystallization from MeOH to separate magenta needles of 2-amino-3-methoxy-5-nonaprenyl-6-methyl-1,4-benzoquinone (rhodoquinone-9) (I, $n=9$) melting at 66—67.5°. IR ν_{max}^{KBr} cm^{-1}: 3450 and 3320 (NH_2), 1668 and 1650 (benzoquinone), 1600 (NH). NMR τ: 4.90 (9H, multiplet, $-CH{=}\overset{|}{C}-$), 5.4 (2H, broad, NH_2), 6.15 (3H, singlet, OCH_3), 6.90 (2H, doublet, ring-CH_2–), 8.0 (35H, side chain $-CH_2-$ and ring-CH_3), 8.28 (3H, *trans* ring-$CH_2-CH{=}\overset{|}{C}-C\underline{H}_3$), 8.35 (3H, *cis* terminal $-CH{=}\overset{|}{C}-C\underline{H}_3$), 8.42 (24H, *trans* $-CH{=}\overset{|}{C}-C\underline{H}_3$) (Fig. 4).

The intensities of two signals at τ 8.28 and 8.35 were almost equal, as those of X (X=Br), consequently it could be concluded that the isoprenyl side chain retained all *trans* configuration.

It was confirmed by IR, NMR spectroscopy and mixed melting point that rhodoquinone-9 (I, $n=9$), thus synthesized, was completely identical with the authentic sample from the natural source.

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20) Aluminum oxide "Woelm neutral (activity grade I)," deactivated with 7% of water in n-hexane, was used.

21) P. Scheudel, H. Mayer, J. Metzger, R. Rüeg, and O. Isler, *Helv. Chim. Acta*, **46**, 2517 (1963).

Experimental[22]

3-Bromo-4-methoxy-5-nitrotoluene (IV, X=Br)——2-Bromo-6-nitro-*p*-cresol (30 g) was well triturated with 42.5 g of Na_2CO_3 in 100 ml of toluene and the suspension was gently refluxed with 33 g of $(CH_3)_2SO_4$ for 2 hr. Additional $(CH_3)_2SO_4$ (33.5 g) was then added and refluxing was continued for a further 2 hr. The cooled reaction mixture was washed with 10% Na_2CO_3 and then water. The organic layer was dried over anhyd. $MgSO_4$, and the solvent was removed *in vacuo* to leave a yellow solid which was recrystallized from 90% MeOH giving 23 g (73%) of IV (X=Br) as pale yellow needles, mp 52—53°. *Anal.* Calcd. for $C_8H_8O_3NBr$: C, 39.05; H, 3.27; N, 5.69. Found: C, 39.16; H, 3.22; N, 5.60.

3-Chloro-4-methoxy-5-nitrotoluene (IV, X=Cl)——A reaction was carried out with 46.5 g of 2-chloro-6-nitro-*p*-cresol, 50 g of Na_2CO_3 and 73 g of $(CH_3)_2SO_4$ in 130 ml of toluene according to the same method as described above. Recrystallization from aqueous MeOH gave 44.2 g (89%) of IV (X=Cl) as pale yellow needles, mp 41—41.5°. *Anal.* Calcd. for $C_8H_8O_3NCl$: C, 47.66; H, 4.00; N, 6.95. Found: C, 47.52; H, 3.97; N, 6.99.

3-Bromo-4-methoxy-5-aminotoluene (V, X=Br)——IV (X=Br) (40 g) was dissolved in 120 ml of concd. HCl and 120 ml of 60% EtOH at 55°. To this solution was added 43 g of zinc dust in small portions over 1.5 hr. The resultant solution was stirred at 70° for 2 hr. After being basified with 30% NaOH, the reaction mixture was extracted with ether. The ethereal extract was washed with water and dried over anhyd. $MgSO_4$. Evaporation of the solvent *in vacuo* gave a dark brown oil of V (X=Br) (25 g, 73.5%). HCl salt (from EtOH): white needles, mp 214° (decomp.). *Anal.* Calcd. for $C_8H_{10}NBr\cdot HCl$: C, 38.05; H, 4.39; N, 5.55. Found: C, 37.68; H, 4.42; N, 5.35.

3-Chloro-4-methoxy-5-aminotoluene (V, X=Cl)——A solution of 39.2 g of IV (X=Cl) and 96 g of $SnCl_2\cdot 2H_2O$ in a mixture of 165 ml of concd. HCl and 240 ml of EtOH was heated under reflux. Dry HCl gas was slowly passed through the solution. After 3.5 hr, the passage of gas was stopped and refluxing was continued for a further 2 hr. The residue from evaporation of the solvent was basified with 30% NaOH and the reaction mixture was extracted with ether. After working up in a similar manner as described above, there was obtained 26 g (78%) of V (X=Cl) as a dark brown oil. HCl salt (from EtOH–H_2O): white flakes, mp 185—200° (sublimation). *Anal.* Calcd. for $C_8H_{10}ONCl\cdot HCl$: C, 46.17; H, 5.32; N, 6.76. Found: C, 45.90; H, 5.24; N, 6.54.

2-Bromo-3-methoxy-6-methyl-1,4-benzoquinone (VI, X=Br)——a) To a stirred solution of 28 g of potassium nitrosodisulfonate in 470 ml of 0.17M aqueous KH_2PO_4 solution and 1400 ml of water was added 8.8 g of V (X=Br) in 150 ml of ether in one portion. The resultant solution was stirred at room temperature for 6 hr, and then extracted with ether. Evaporation of the solvent gave a crude liquid of VI (X=Br) which was purified by chromatography on silica gel (100 g). Elution with *n*-hexane–ether (95:5) gave a yellow solid. Recrystallization from petroleum ether yielded 2.7 g (37.6%) of VI (X=Br) as orange yellow needles, mp 62—63°. *Anal.* Calcd. for $C_8H_7O_3Br$: C, 41.59; H, 3.05. Found: C, 41.87; H, 3.04. Further elution with *n*-hexane–ether (3:2) afforded 1.2 g of V (X=Br).

b) To a stirred suspension of 9 g of V (X=Br) in a mixture of 30 ml of acetone and 100 ml of 30% H_2SO_4 was added dropwise a solution of 14.7 g of $Na_2Cr_2O_7$ in 80 ml of water over 2 hr under cooling below −5°. The reaction mixture was stirred for a further 2 hr at −5°. After being allowed to stand overnight in ice-box, the solution was extracted with petroleum ether, and the organic layer was washed with water and dried over anhyd. $MgSO_4$. After removal of the solvent *in vacuo*, the residue was chromatographed over silica gel (40 g). After working up in a similar manner as described above, there was obtained 2.1 g (21.5%) of VI (X=Br) as orange yellow needles, mp 62—63°.

2-Chloro-3-methoxy-6-methyl-1,4-benzoquinone (VI, X=Cl)——A suspension of 15 g of V (X=Cl) in 30 ml of acetone and 125 ml of 30% H_2SO_4 was treated with a solution of 17.5 g of $Na_2Cr_2O_7$ in 100 ml of water under a similar condition as described in b) of VI (X=Br). Recrystallization from petroleum ether gave 5 g (30.6%) of VI (X=Cl) as orange yellow needles, mp 58.5—59.3°. *Anal.* Calcd. for $C_8H_7O_3Cl$: C, 51.49; H, 3.78. Found: C, 51.57; H, 3.73.

2-Bromo-3-methoxy-6-methyl-1,4-hydroquinone (IX, X=Br)——A solution of VI (X=Br) in 20 ml of ether was reduced by shaking with saturated aqueous $Na_2S_2O_4$ solution until the solution became colorless. The organic layer was separated and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a solid which was recrystallized from *n*-hexane to separate colorless needles of IX (X=Br) in almost quantitative yield, mp 102.5—103.5°. *Anal.* Calcd. for $C_8H_9O_3Br$: C, 41.22; H, 3.89. Found: C, 41.42; H, 3.81. NMR τ: 3.22 (1H, singlet, ring-H), 4.70 (1H, singlet, OH), 4.78 (1H, singlet, OH), 6.14 (3H, singlet, OCH_3), 7.77 (3H, singlet, CH_3).

2-Chloro-3-methoxy-6-methyl-1,4-hydroquinone (IX, X=Cl)——An experiment was carried out essentially by the same method as described above. Recrystallization from petroleum ether–ether gave colorless

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22) Melting points are uncorrected and were obtained with a micro melting point apparatus (Yanagimoto MP-S2).

plates in almost quantitative yield, mp 108.5—109.5°. *Anal.* Calcd. for $C_8H_9O_3Cl$: C, 50.94; H, 4.81. Found: C, 51.06; H, 4.82.

2-Amino-3-methoxy-6-methyl-1,4-benzoquinone (I, $n=0$)——VI (X=Br) (100 mg) and 50 mg of NaN_3 in 5 ml of 80% MeOH were stirred at room temperature for 1 hr. During this time, the solution became deep red. The mixture was extracted with 10 ml of $CHCl_3$ and the extract was shaken with saturated aqueous $Na_2S_2O_4$ solution until the organic layer changed from red to colorless. The $CHCl_3$ layer was separated and dried over anhyd. $MgSO_4$. To this solution was added 5 ml of 1,1,2-trichloroethane and the resultant solution was refluxed under nitrogen for 5 hr. Evaporation of the solvent *in vacuo* gave the crude (I, $n=0$) which was dissolved in a small amount of *n*-hexane–ether (4:1) and transferred to a column of silica gel (10 g). Elution with *n*-hexane–ether (98:2) gave a brown solid, which was not investigated. Further development of the column with *n*-hexane–ether (95:5) gave traces of impurities, and the violet-colored band was finally eluted with *n*-hexane–ether (9:1) to afford I ($n=0$) as a solid. Recrystallization from *n*-hexane yielded 18 mg (24.8%) of dark violet needles, mp 91°. *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.45; H, 5.42; N, 8.38. Found: C, 57.38; H, 5.37; N, 8.51.

Reaction of Ammonia with (VI, X=Br)——A solution of 340 mg of VI (X=Br) in a mixture of 50 ml of ether and 20 ml of MeOH was stirred under cooling below 0° and dry NH_3 gas was introduced thereto during 15 min. Stirring was continued for a further 15 min and the resulting mixture was concentrated *in vacuo*. The residue was taken up in a small portion of ether and chromatographed over silica gel (5g). Elution with *n*-hexane–ether (95:5) afforded 70 mg of the starting material. Further development of the column with *n*-hexane–ether (85:15) gave a violet solid which was recrystallized from petroleum ether–ether to separate 50 mg of VII as reddish violet needles, mp 152—153.5°. *Anal.* Calcd. for $C_7H_6O_2NBr$: C, 38.91; H, 2.80; N, 6.48. Found: C, 39.12; H, 2.78; N, 6.59. The mother liquor was concentrated *in vacuo* to yield a solid. Recrystallization from petroleum ether gave yellow prisms of VIII (100 mg), mp 80—81°. TLC[23] [$CHCl_3$]: single spot, *Rf*=0.57. *Anal.* Calcd. for $C_9H_{11}O_4Br$: C, 41.08; H, 4.12; N, 0; mol. wt., 263. Found: C, 41.39; H, 4.17; N, 0; mol. wt,[19] 267.

2-Bromo-3-methoxy-5-nonaprenyl-6-methyl-1,4-benzoquinone (X, X=Br)——IX (X=Br) (1.0 g) and 0.5 ml of $BF_3\cdot$ether were dissolved in 2 ml of absol. dioxane under nitrogen at 55—60° (bath temperature). To this solution was dropped 1.8 g of solanesol in 0.8 ml of absol. dioxane over 1 hr and the mixture was then heated with stirring at 60—65° for 1 hr. The cooled reaction mixture was diluted with 50 ml of petroleum ether and the petroleum ether solution was extracted well four times with 75% MeOH (20 ml each). The MeOH layer was re-extracted with petroleum ether. The combined petroleum ether extract was washed with water and dried over anhyd. $MgSO_4$. After removal of the solvent *in vacuo*, the residue was dissolved in ether, and the resultant solution was oxidized with 3 g of Ag_2O at room temperature for 1.5 hr. The inorganic material was filtered off, and the filtrate gave the crude X (X=Br) which was dissolved in a small amount of *n*-hexane and charged on a column of aluminum oxide (50 g) and developed with *n*-hexane and *n*-hexane–ether (98:2) successively. The elute with *n*-hexane–ether was evaporated *in vacuo* to give X (X=Br) as a yellow semi-solid which was dissolved in *n*-hexane and re-chromatographed on silica gel (50 g). Elution with *n*-hexane–ether (98:2) gave a yellow oil, which failed to crystallize and was not investigated. Further development of the column with *n*-hexane–ether (97:3) yielded 400 mg of X (X=Br). Recrystallization from ether–MeOH afforded 150 mg (10.4%) of yellow grains, mp 37—39°. TLC ($CHCl_3$–*n*-hexane (4:1)): single spot, *Rf*=0.86. *Anal.* Calcd. for $C_{53}H_{79}O_3Br$: C, 75.41; H, 9.43. Found: C, 75.49; H, 9.39. The above MeOH layer was poured into water (500 ml) and the solution was extracted with ether followed by oxidation with Ag_2O to give 0.4 g of VI (X=Br).

2-Chloro-3-methoxy-5-nonaprenyl-6-methyl-1,4-benzoquinone (X, X=Cl)——To a stirred solution of 2.4 g of IX (X=Cl) and 0.3 ml of $BF_3\cdot$ether in 10 ml of absol. dioxane, 4.1 g of solanesol in 4 ml of absol. dioxane was dropped over 2 hr under nitrogen at 50—55° (bath temperature). The reaction mixture was then heated at 55—60° for a further 1 hr. After working up in a similar manner as described above, there was obtained 650 mg (15%) of X (X=Cl) as a semi-solid. The recovery of VI (X=Cl) from the MeOH layer was 1.4 g.

2-Amino-3-methoxy-5-nonaprenyl-6-methyl-1,4-benzoquinone (I, $n=9$)——a) A solution of 50 mg of X (X=Br) and 25 mg of NaN_3 in a mixture of 3 ml of ether and 2 ml of MeOH was refluxed under nitrogen for 5 hr and the solvent was evaporated *in vacuo*. The residue was dissolved in 10 ml of ether and reduced by shaking with saturated $Na_2S_2O_4$ solution until the resultant solution changed from red to coorless. The residue from the ethereal layer was taken up into 5 ml of 1,1,2-trichloroethane and the solution was refluxed under nitrogen for 2 hr. After removal of the solvent *in vacuo*, the residue was dissolved in small amounts of *n*-hexane, and the solution was poured on a column of silica gel (10 g), developed with *n*-hexane, *n*-hexane–ether (98:2) and *n*-hexane–ether (95:5) successively. The violet-colored band was finally eluted with *n*-hexane–ether (92.5:7.5). A solid obtained from the elute was recrystallized from MeOH to yield 10 mg

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23) TLC was carried out using silica gel G (E. Merck AG.) plates having a 1 mm layer. The plates were dried at room temperature overnight and activated for 3 hr at 80°. Spots were detected by iodine vapour.

(21.6%) of I ($n=9$) as magenta needles, mp 66—67.5°. TLC [$CHCl_3$]: single spot, $Rf=0.5$. *Anal.* Calcd. for $C_{53}H_{81}O_3N$: C, 81.59; H, 10.47; N, 1.80. Found: C, 81.97; H, 10.48; N, 1.49.

b) A solution of 350 mg of X (X=Cl) and 100 mg of NaN_3 in a mixture of 10 ml of ether and 5 ml of 80% MeOH was refluxed under nitrogen for 5 hr and the resulting mixture was treated with ether. The ethereal layer was reduced by shaking with saturated aqueous $Na_2S_2O_4$ solution until the resulting solution became essentially colorless. The organic layer was separated and dried over anhyd. $MgSO_4$. The residue obtained upon removal of the solvent was dissolved in 15 ml of $CHCl_3$ and the solution was refluxed under nitrogen for 2 hr. The following procedure was the same as described above. Recrystallization from MeOH gave 75 mg (21.8%) of I ($n=9$) as magenta needles, mp 66.5—67.5°, which was identical with the sample obtained in a) in all respects.

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