

Anal. Calcd. for $C_8H_{10}O_2NCl$: C, 51.21; H, 5.37; N, 7.47. Found: C, 51.13; H, 5.21; N, 7.62.

This epoxy compound, XIV, was obtained in small yields when 1-g. quantities of vitamin B₆, XI, and its ethyl ether, VIII, were treated with 15 cc. of 50% sulfuric acid for one hour on the steam-bath. The sulfuric acid was neutralized with sodium hydroxide, the water was evaporated, and the product was extracted with acetone as the free base. The addition of dry hydrogen chloride gave a product which, after crystallization from alcohol, was identical with the by-product described above.

Cleavage of the Epoxydimethyl Group.—2-Methyl-3-hydroxy-4,5-(epoxydimethyl)-pyridine resisted hydrolysis on heating with 2.5 *N* hydrochloric acid at 175° for four hours. However, the ether group was split when 3.7 g. of the epoxydimethyl derivative, XIV, was distilled with 60 cc. of 48% hydrobromic acid until the volume was reduced to 30 cc. After cooling and filtering, the yield of 2-methyl-3-hydroxy-4,5-*bis*-(bromomethyl)-pyridine hydrobromide, XII, was 6.42 g. (86.5%); m. p. 228.5°. This melting point was 5° higher than previously reported.³

Anal. Calcd. for $C_8H_{10}NOBr_3$: C, 25.53; H, 2.66; N, 3.72. Found: C, 25.71; H, 2.89; N, 3.73.

Acknowledgment.—The authors are indebted to Messrs. D. F. Hayman and W. Reiss for the microanalyses and to Mr. A. N. Wilson for technical assistance.

Summary

Variations and improvements in the synthesis of vitamin B₆ have been made. The compounds 2-methyl-3-hydroxy-4-ethoxymethyl-5-hydroxymethylpyridine and 2-methyl-3-amino-4-ethoxymethyl-5-aminomethylpyridine have been hydrolyzed directly to the corresponding hydroxy derivatives by heating with dilute hydrochloric acid at 150–175° under pressure. Derivatives of some of the intermediates and a new inner ether of vitamin B₆ have been described.

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[CONTRIBUTION FROM THE SANDERS LABORATORY OF CHEMISTRY, VASSAR COLLEGE, AND THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Reaction between 2,3-Dimethyl-1,4-naphthoquinone and Phenylmagnesium Bromide. II¹

BY H. MARJORIE CRAWFORD

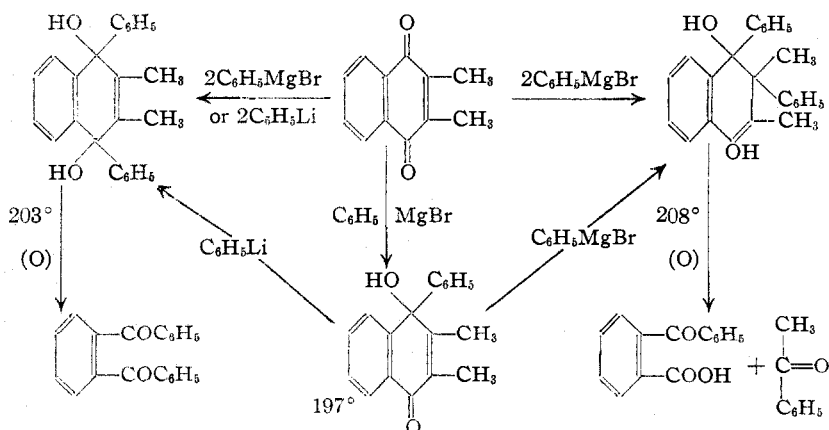
In an earlier paper² it was shown that phenylmagnesium bromide reacts with 2,3-dimethyl-1,4-naphthoquinone to give all of the expected reduction and addition products. These solids accounted for about 30% of the starting material, the other product being a dark, thick oil. No amorphous materials were encountered. Four addition products were described, two resulting from the 1,2- and 1,4-addition of one molecule of phenylmagnesium bromide to one molecule of the quinone, and two resulting from the 1,2-1,2- and 1,2-1,4-addition of two molecules of phenylmagnesium bromide to one molecule of the quinone.

Further reactions of the two di-addition products are described in this paper.

(1) Reported at the fall meeting of the American Chemical Society at Boston, Mass., September, 1939.

(2) Crawford, *THIS JOURNAL*, **57**, 2000 (1935).

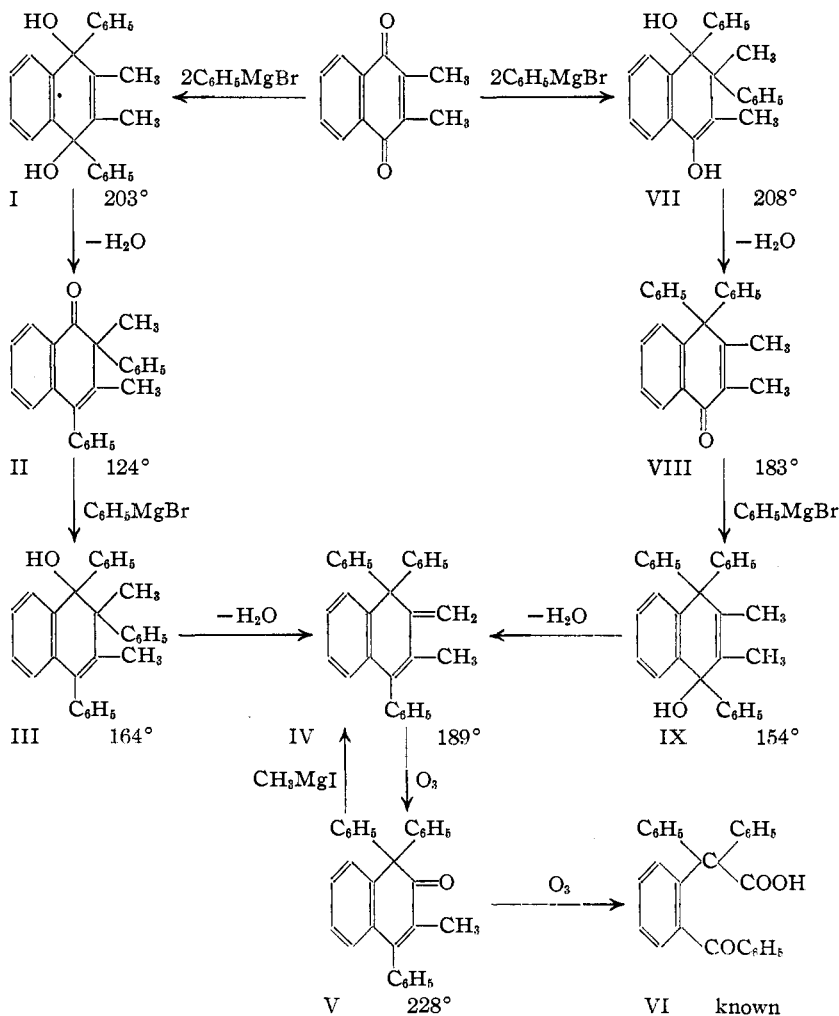
The structures of the two di-addition products were established as shown by the following equations.



In the Grignard machine, both di-addition compounds showed two active hydrogens. Oxidation of both compounds gave known products which served to locate the phenyl groups. The 203° compound gave *o*-dibenzoylbenzene and the 208° compound gave acetophenone and *o*-benzoyl-

benzoic acid. The 203° compound was also formed by the reaction of phenyllithium on either the 197° mono-addition compound or the original quinone. Phenylmagnesium bromide reacted with the 197° mono-addition compound to give the 208° compound.

Starting with these two di-addition products, parallel series of reactions led to the same product, a hydrocarbon.



The dehydration and rearrangement of I led to the formation of the 124° compound (II). II was oxidized easily to acetophenone and *o*-benzoylbenzoic acid. The formation of these products indicated that the formation of II from I involved the shift of one phenyl group from a carbon next to the ring to a carbon holding a methyl group. Very small amounts of II were available and the only other reactions investigated were those with phenyllithium and with phenylmagnesium bro-

me. In both of these reactions, decomposition of the metallic product with acid led to the formation of a hydrocarbon (IV). Careful decomposition of the metallic compound with water gave an intermediate carbinol (III) which, in the presence of acid, easily lost a molecule of water and gave the hydrocarbon. This hydrocarbon was difficult to oxidize with ordinary oxidizing agents, but was attacked readily by ozone to give formaldehyde and a ketone

(V). When the ketone was treated with methylmagnesium iodide followed by acid, the hydrocarbon was formed again, so no rearrangement occurred during the reaction with ozone. Ozonization of the ketone (V) gave a known keto acid (VI). The structure of this known keto acid located the three phenyl groups in the hydrocarbon (IV) and in the ketone (V).

The same hydrocarbon (IV) was obtained by starting with the other di-addition product (VII) and carrying out the same series of reactions. Dehydration of VII gave the 183° compound (VIII) which was extremely unreactive. VIII was recovered unchanged after attempts at oxidation with potassium dichromate or chromium trioxide in glacial acetic acid, with basic potassium permanganate, with hydrogen peroxide and with ozone. The only reactions which VIII could be made to undergo were reduction with zinc and acetic acid (which gave very small amounts of two reduction products) and the reaction with organo-metallic reagents. When phenylmagnesium bromide or phenyllithium was added to VIII and the metallic compound was decomposed with acid, the hydrocarbon (IV) resulted, but if ammonium chloride was used for the decomposition, an intermediate carbinol (IX) could be isolated. Both ozonization of this carbinol and oxidation with potassium

dichromate in acetic acid gave the same products that would have been obtained from the hydrocarbon, so the first reaction was apparently dehydration and this was followed by oxidation.

Knowing the structures of I, II, IV and VII, the structure proposed for VIII seems the only reasonable one, although all attempts to break it up by oxidation and all attempts to synthesize it have so far proved unsuccessful.

The reactions involved in these dehydrations and rearrangements are all of the pinacol and allylic types. Cases of dehydration accompanied by the migration of a phenyl group are not unusual. The researches of Ramart and Amagat,³ Bachmann,⁴ and Kleinfeller and Eckert⁵ showed that, in the cases studied, the phenyl group was the only one to migrate. The tendency of phenyl groups to migrate in preference to methyl groups is shown by the work of McKenzie and Myles⁶ and of Orekhov and Tiffeneau.⁷

In most attempts at oxidation of the carbinol (IX) and of the hydrocarbon (IV), either by potassium permanganate, potassium dichromate or ozone, there resulted small amounts of a hydrocarbon, melting at 235°, which was isomeric with the hydrocarbon (IV). An oil was formed when this hydrocarbon was treated with ozone and no structure can be suggested for it at this time.

Experimental

All combustions were carried out using the semi-micro method of Lauer and Dobrovoiny.⁸ Molecular weight determinations were made by the lowering of the freezing point of benzene or of camphor.

1,4 - Dioxy - 2,3 - dimethyl - 1,4 - diphenyldihydronaphthalene, I, m. p. 203–204°.—Because of its great solubility, this white di-addition product was obtained only occasionally from the mixture of products resulting from the reaction between phenylmagnesium bromide and 2,3-dimethyl-1,4-naphthoquinone. When it was obtained from this mixture, it was in the form of a pale yellow double compound which contained two molecules of the quinone to one molecule of the 203° compound. The quinone could be steam distilled from a solution of the double compound leaving the 203° compound (I). I was obtained in much better yields (20%) by the reaction of 0.2 mole of phenyllithium⁹ on 0.1 mole (18.6 g.) of the quinone. The green solid formed in this reaction looked very much like the solid formed during the reaction between phenyl-

magnesium bromide and the quinone. After standing for two hours, the mixture was decomposed with ice and dilute hydrobromic acid. The organic material was extracted with ether. Evaporation of the ether gave 10 g. of white solid which after recrystallization from 50% alcohol yielded 6.85 g. of I. This compound was also formed, in 50% yield, by the reaction of 0.02 mole of phenyllithium on 0.01 mole of the 197° mono-addition compound.

The Grignard machine showed two active hydrogens. The other analytical data are included in the earlier paper² (in which the 203° compound was numbered IX).

Potassium permanganate was not decolorized and heating 1.0 g. of I for one and one-half hours with potassium dichromate gave a small amount of solid melting at 140–143°. Better results were obtained by adding 2.0 g. of I to 2.0 g. of chromium trioxide in 10 cc. of glacial acetic acid and boiling for five minutes. Pouring the mixture immediately into water gave a precipitate which on crystallization from alcohol melted at 145–148° and was identical with a known sample of *o*-dibenzoylbenzene.

Heating I with hydrochloric acid in methyl alcohol or with zinc chloride and hydrochloric acid in benzene caused it to lose a molecule of water and to be transformed almost quantitatively into the 124° compound (II).

1 - Oxo - 2,3 - dimethyl - 2,4 - diphenyldihydronaphthalene, II, m. p. 124°.—This compound was obtained once in the crystallization of the yellow double compound of I and quinone. Later it was easily obtained, in practically quantitative yields, by the dehydration of I.

Oxidation of 1.0 g. of II by boiling for five hours with 3.0 g. of potassium dichromate in glacial acetic acid gave acetophenone and *o*-benzoylbenzoic acid. II decolorized bromine in carbon tetrachloride slowly, but failed to give a semicarbazone. It reacted readily with phenylmagnesium bromide and phenyllithium. When the metallic product was decomposed by acid (after fifteen minutes of standing) there resulted a hydrocarbon (IV). When the metallic product was decomposed carefully with water, a carbinol (III) was obtained.

The analytical data for II are contained in the earlier paper² (in which the 124° compound was numbered XI).

1 - Oxy - 2,3 - dimethyl - 1,2,4 - triphenyldihydronaphthalene, III, m. p. 164–174°.—This carbinol was prepared by adding phenylmagnesium bromide in excess to 0.7 g. of II, decomposing the product with water, and extracting with ether. The small amount of solid from the ether solution was crystallized from alcohol, in which it was quite soluble, and melted at 164–174°. Heating in benzene for one hour with a few crystals of zinc chloride and five drops of concd. hydrochloric acid caused 0.2 g. of III to lose water with the formation of the hydrocarbon (IV).

Anal. Calcd. for C₃₀H₂₆O: C, 89.51; H, 6.51. Found: C, 88.92, 88.83; H, 6.80, 6.65.

3 - Methyl - 2 - methylene - 1,1,4 - triphenyldihydronaphthalene, IV, m. p. 189–190°.—This hydrocarbon was obtained by the dehydration of either of the carbinols, III or IX. Addition of methylmagnesium iodide to 0.25 g. of the ketone (V) and decomposition of the reaction mixture with hydrochloric acid also gave the hydrocarbon in 76% yield. The best method of preparation, giving practically quantitative yields, was the addition of phenylmagnesium bromide to the 183° compound (VIII) and decomposition

(3) Ramart and Amagat, *Ann. chim.*, **8**, 263 (1927).

(4) Bachmann, *THIS JOURNAL*, **54**, 1969 (1932).

(5) Kleinfeller and Eckert, *Ber.*, **62**, 1598 (1929).

(6) McKenzie and Myles, *ibid.*, **65**, 209 (1932).

(7) Orekhov and Tiffeneau, *Compt. rend.*, **182**, 67 (1926).

(8) Lauer and Dobrovoiny, *Mikrochem., Pregl Festschr.*, **243** (1929).

(9) Gilman, *THIS JOURNAL*, **54**, 1957 (1932).

of the reaction mixture, after about an hour, with hydrochloric acid. The hydrocarbon was then extracted with ether, the solvent evaporated, and the solid crystallized from a mixture of alcohol and benzene. It was only slightly soluble in isopropyl ether, alcohol and ethyl acetate but was very soluble in benzene. It decolorized bromine in carbon tetrachloride rapidly.

Potassium permanganate in acetone was not decolorized by IV at room temperature. When the hydrocarbon was boiled for four hours with potassium dichromate in glacial acetic acid, a small amount of benzoic acid was isolated along with a neutral oil which could not be crystallized. Ozonization of IV in chloroform or in carbon tetrachloride gave varying results. The solution of the ozonide was poured into water and allowed to stand overnight. The main product from the ether extract was always the ketone (V) with sometimes small amounts of the keto acid (VI) and sometimes small amounts of a hydrocarbon, m. p. 235°. In one case the ozonide was dropped into boiling water containing zinc dust and traces of hydroquinone and silver nitrate. The resulting gases were passed into a solution of methone and there were formed white needles of formaldimethone, identical with synthetic formaldimethone.

Anal. Calcd. for $C_{30}H_{24}$ (384.2): C, 93.71; H, 6.29. Found: C, 93.71, 93.26; H, 6.28, 6.66; mol. wt. (benzene) 360, (camphor) 398, 416.

2 - Oxo - 3 - methyl - 1,1,4 - triphenyldihydronaphthalene, V, m. p. 228°.—This ketone was formed by ozonizing the hydrocarbon (IV) and the carbinol (IX). It is only slightly soluble in alcohol, glacial acetic acid and pyridine, but is fairly soluble in hot benzene. It decolorized bromine in carbon tetrachloride rapidly. Fusion with potassium hydroxide, treatment with semicarbazide and boiling for three hours with potassium dichromate in glacial acetic acid gave only unchanged material. Addition of excess methylmagnesium iodide to 0.25 g. of the ketone and decomposition of the mixture with ice and hydrochloric acid gave 0.19 g. (76%) of the hydrocarbon (IV). Ozonization of 1.0 g. of the ketone in carbon tetrachloride and decomposition of the ozonide with water gave 0.6 g. of a white acid (VI) which decomposed at 218°.

Anal. Calcd. for $C_{29}H_{22}O$: C, 90.11; H, 5.74. Found: C, 90.16; H, 5.95.

Diphenyl-(*o*-benzoylphenyl)-acetic Acid, VI.—This keto acid was obtained by ozonizing the ketone (V). It was recrystallized from benzene and acetone and decomposed at 218°. The acid was transformed into the methyl ester by boiling about 0.3 g. of the acid with 5 cc. of methyl alcohol and two drops of concd. sulfuric acid. A white precipitate formed after forty minutes and the solution was cooled and filtered. The ester melted at 189–190°. This keto acid was then synthesized by the oxidation of 1,1,3-triphenylindene.¹⁰ The methyl ester of this acid had not been reported before and was made by boiling 1.0 g. of the synthetic acid with 20 cc. of methyl alcohol and six drops of concd. sulfuric acid. As in the other case, solid separated after about forty minutes of heating. The solid melted at 188–189° and after recrystallization from methyl alcohol and benzene finally melted at 192–193°.

(10) Kohler. *Am. Chem. J.*, **40**, 291 (1908).

The mixed melting point of this ester with that from the acid resulting from the ozonization of the ketone, was 190.5–192°.

Anal. Calcd. for $C_{28}H_{22}O_2$: C, 82.73; H, 5.45. Found: C, 82.63; H, 5.56.

1,4 - Dioxy - 2,3 - dimethyl - 1,2 - diphenyldihydronaphthalene, VII, m. p. 208–209°.—This compound was the main solid product from the reaction between phenylmagnesium bromide and 2,3-dimethyl-1,4-naphthoquinone.² It also resulted from the reaction of phenylmagnesium bromide on the 197° mono-addition compound. It was oxidized easily to acetophenone and *o*-benzoylbenzoic acid by boiling for five hours with potassium dichromate and glacial acetic acid. The Grignard machine showed two active hydrogens. The most interesting reaction of VII was the loss of a molecule of water to give the 183° compound (VIII). This reaction could be brought about by treatment with various reagents. Heating on the steam-bath for two hours with phosphorus tribromide in bromoform, heating for six hours in benzene with about 3 g. of zinc chloride and 3 cc. of concd. hydrochloric acid or heating for one hour with 0.5 g. of iodine in 50 cc. of glacial acetic acid transformed 1.0 g. of VII into VIII in 90% yields. VII was not changed by one-half hour of heating with 20% sulfuric acid nor by warming on the steam-bath with acetic anhydride and sodium acetate.

Other properties and analytical data are included in the earlier paper² (in which this compound was numbered VI).

4 - Oxo - 2,3 - dimethyl - 1,1 - diphenyldihydronaphthalene, VIII, m. p. 183°.—This compound was formed in about 90% yields by the loss of a molecule of water from compound VII. It is very soluble in most organic solvents and separates from hot alcohol in glistening white leaflets. Its extreme inertness is its most outstanding characteristic. It was recovered unchanged from boiling for one hour with constant boiling hydrobromic acid, from boiling for seven hours with hydroxylamine, from warming for one hour with semicarbazide, from warming with phenylhydrazine and 2,4-dinitrophenylhydrazine, from warming with aluminum isopropylate, from warming with potassium permanganate and potassium hydroxide, from boiling for five hours with potassium dichromate in glacial acetic acid, from boiling for one hour with chromium trioxide in glacial acetic acid, from warming for six hours with 30% hydrogen peroxide, and from ozonizing for one hour in carbon tetrachloride. It does not decolorize bromine in carbon tetrachloride.

Reduction of 3.2 g. of VIII by boiling for four hours with 5 g. of zinc and 25 cc. of glacial acetic acid gave very small amounts of two neutral products. One melted at 142–143° and analyses corresponded to the addition of two atoms of hydrogen to give the compound $C_{24}H_{22}O$. The other melted at 176–177° and is a hydrocarbon.

The only reactions that took place readily were those with phenylmagnesium bromide and phenyllithium. The Grignard machine showed the addition of one molecule of methylmagnesium iodide and no active hydrogens. When the mixture from the reaction of either phenylmagnesium bromide or phenyllithium on VIII was decomposed with hydrochloric acid, the hydrocarbon (IV) was isolated in 90% yields from the ether extract. If the magnesium compound was carefully decomposed, after about twenty

minutes, with ammonium chloride and water, the ether extract gave 90% yields of the carbinol (IX).

Other analytical data on this compound are contained in the earlier paper² (in which this compound was numbered VIII).

4 - Oxy - 2,3 - dimethyl - 1,1,4 - triphenyldihydronaphthalene, IX, m. p. 154°.—This carbinol was formed in 90% yields by the addition of phenylmagnesium bromide to VIII. It is very unstable in the presence of acid and when an alcohol solution of the carbinol was treated with hydrochloric acid, a molecule of water was lost with the formation of the hydrocarbon (IV). IX melts at 154° with the loss of a molecule of water and the formation of the hydrocarbon (IV). Warming with zinc chloride and concd. hydrochloric acid in benzene also converted IX to the hydrocarbon (IV). The Grignard machine showed one active hydrogen. Boiling for one hour with potassium permanganate and potassium hydroxide gave 90% of unchanged material. Boiling for one hour with potassium dichromate in glacial acetic acid gave a solid from which, after many recrystallizations from alcohol and ethyl acetate, it was possible to isolate a small amount of the 235° hydrocarbon. Ozonization of IX in chloroform gave the ketone (V), so dehydration to the hydrocarbon (IV) probably occurred before the reaction with ozone.

Anal. Calcd. for $C_{30}H_{26}O$: C, 89.51; H, 6.51. Found: C, 89.31, 88.95; H, 6.80, 6.75.

The 235° Hydrocarbon.—This compound, isomeric with the 189° hydrocarbon (IV), was formed in small amounts in many attempts to oxidize the hydrocarbon (IV) with potassium dichromate or potassium permanganate in glacial acetic acid or with ozone, and to oxidize the

carbinol (IX) with potassium dichromate in glacial acetic acid.

Heating the hydrocarbon (IV) with acetic acid alone or with iodine in acetic acid did not convert it into the high melting isomer. Ozone converted 0.4 g. of the 235° compound into an oil from which no solid material could be obtained. The 235° compound was only slightly soluble in alcohol and in ethyl acetate, but could be crystallized from benzene.

Anal. Calcd. for $C_{30}H_{24}$ (384.2): C, 93.71; H, 6.29. Found: C, 93.84, 93.23; H, 6.29, 6.07; mol. wt. (camphor), 360.

The author wishes to thank the University of Minnesota for the courtesy shown her as an Honorary Fellow of the University while on leave from Vassar College in the spring of 1938.

Summary

Starting with the two di-addition products from the reaction between phenylmagnesium bromide and 2,3-dimethyl-1,4-naphthoquinone, parallel series of reactions lead to the same product, a hydrocarbon.

Structures have been assigned to these two di-addition products, to the two compounds resulting from the dehydration and rearrangement of these compounds, and to four new compounds obtained in these series of reactions.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. LXXVI. Oxidation and Reduction Products of Equilenin

BY RUSSELL E. MARKER AND EWALD ROHRMANN

In previous work¹ from this Laboratory it was observed that equilenin when reduced with Adams catalyst in acidic ethanol gave approximately a 70% yield of 5,7,9-estratrienol-17. No other reduction products were isolated. Ruzicka, Müller and Mörgeli² in a somewhat similar reduction obtained this same product in addition to some α -dihydroequilenin. By modifying the reduction technique these workers were able to obtain a 5,7,9-estratrienediol-3,17 which was identical with one of the diols obtained by the reduction of equilenin with sodium.^{2,3,4}

(1) Marker, Kamm, Oakwood and Tendick, *THIS JOURNAL*, **59**, 768 (1937).

(2) Ruzicka, Müller and Mörgeli, *Helv. Chim. Acta.*, **21**, 1394 (1938).

(3) Marker, Rohrmann, Wittle and Tendick, *THIS JOURNAL*, **60**, 2440 (1938).

(4) David, *Acta Brevia Neerland. Physiol. Pharmacol. Microbiol.*, **8**, 211 (1938).

When the hydrogenation of equilenin is carried out in a neutral medium with Adams catalyst, the essential product is α -dihydroequilenin, a product first isolated from the phenolic fraction of mares pregnancy urine by Wintersteiner and co-workers⁵ and later prepared by Marker and co-workers¹ by the reduction of equilenin with aluminum isopropylate. The hydrogenation of α -dihydroequilenin in acidic ethanol yields the same 5,7,9-estratrienol-17 as was obtained from equilenin, indicating that the hydroxyl group at C-17 is of the α -configuration.

In a previous comprehensive investigation of the carbinol fraction of mares pregnancy urine⁶ we reported the isolation (from the chromic anhy-

(5) Wintersteiner, Schwenk, Wirschmann and Whitman, *THIS JOURNAL*, **58**, 2652 (1936).

(6) Marker and Rohrmann, *THIS JOURNAL*, **61**, 2537 (1939).