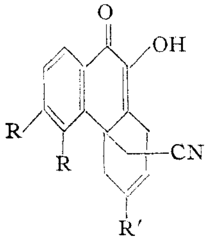
[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

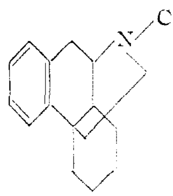
The Synthesis of Ring Systems Related to Morphine. III. 5,6-Dimethoxy-4-cyanomethyl-1,2-naphthoquinone and its Condensation with Dienes

BY MARSHALL GATES*

Earlier papers in this series[1] have dealt with the diene synthesis of 9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (I)[2] and its conversion to a substance (II) having the carbon–nitrogen skeleton of morphine or stereoisomeric with it.



I, R,R′ = H
III, R = OCH_3, R′ = H
IV, R = OCH_3, R′ = Cl
V, R = OCH_3, R′ = OC_2H_5



II

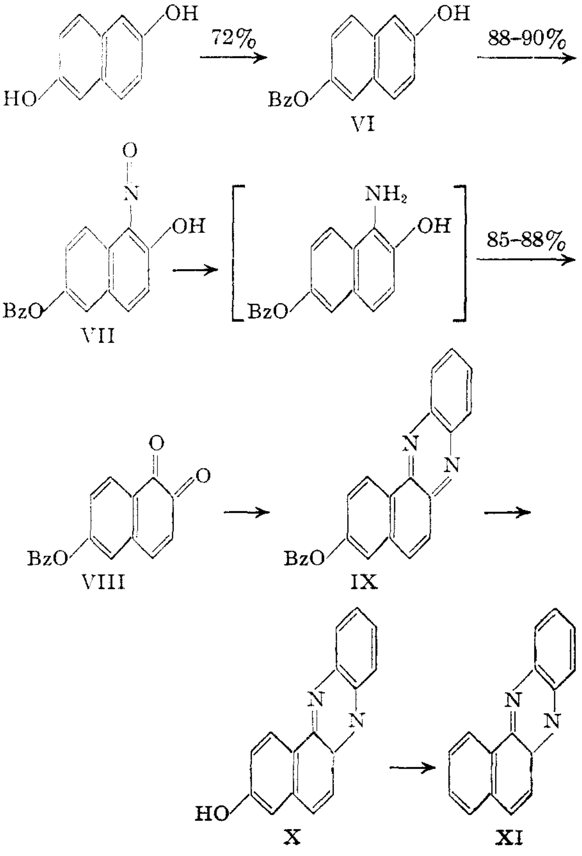
The present report is concerned with the synthesis of 5,6-dimethoxy-4-cyanomethyl-1,2-naphthoquinone and its condensation with butadiene, chloroprene and 2-ethoxybutadiene to yield the 3,4-dimethoxy-9,10-dioxo-13-cyanomethyl - 5,8,9,10,13,14 - hexahydrophenanthrene derivatives III, IV and V.

2,6-Dihydroxynaphthalene, prepared essentially as described by Willstätter and Parnas,[3] served as the starting point for this synthesis. Benzoylation of this substance by the Schotten–Baumann technique yields only the dibenzoate, but a procedure which produces the monobenzoate (VI) in yields as high as 71% was developed, making use of anhydrous dioxane as solvent and somewhat less than one mole of pyridine as catalyst. The dibenzoate is very difficultly soluble in boiling alcohol, and a nearly quantitative separation of the mono and dibenzoates is readily achieved with this solvent.

Nitrosation of the monobenzoate in aqueous acetic acid produces 6-benzoyloxy-1-nitroso-2-naphthol (VII) in 88–90% yield. Conversion of this nitroso compound to pure 6-benzoyloxy-1,2-naphthoquinone (VIII) can be accomplished smoothly in 85–88% yield by catalytic reduction to the corresponding aminonaphthol followed by oxidation with ferric chloride without isolation of the aminonaphthol. A rigorous proof that nitrosation of VI occurs in the 1 position and that the product of reduction and oxidation of this nitroso compound has the structure assigned VIII is afforded by the conversion of VIII to benzo[a]phenazine (XI) through the intermediate 3-benzoyloxy- (IX) and 3-hydroxy- (X) compounds.

The quinone VIII can be reduced in high yield to the hydroquinone XII by means of sulfur dioxide and methylation of this hydroquinone with dimethyl sulfate and potassium carbonate in acetone affords 5,6-dimethoxy-2-naphthol benzoate (XIII) in yields of 82–86%. Short alkaline hydrolysis of this benzoate followed by distillation of the crude material yields pure 5,6-dimethoxy-2-naphthol (XIV) in 80% yield.

The steps nitrosation and conversion to the 1,2-quinone through the aminonaphthol, described above for the monobenzoate of 2,6-dihydroxynaphthalene, when applied to 5,6-dimethoxy-2-naphthol produce pure 5,6-dimethoxy-1,2-naphthoquinone (XV). Yields for the two steps are 97 and 89%, respectively. This quinone gives



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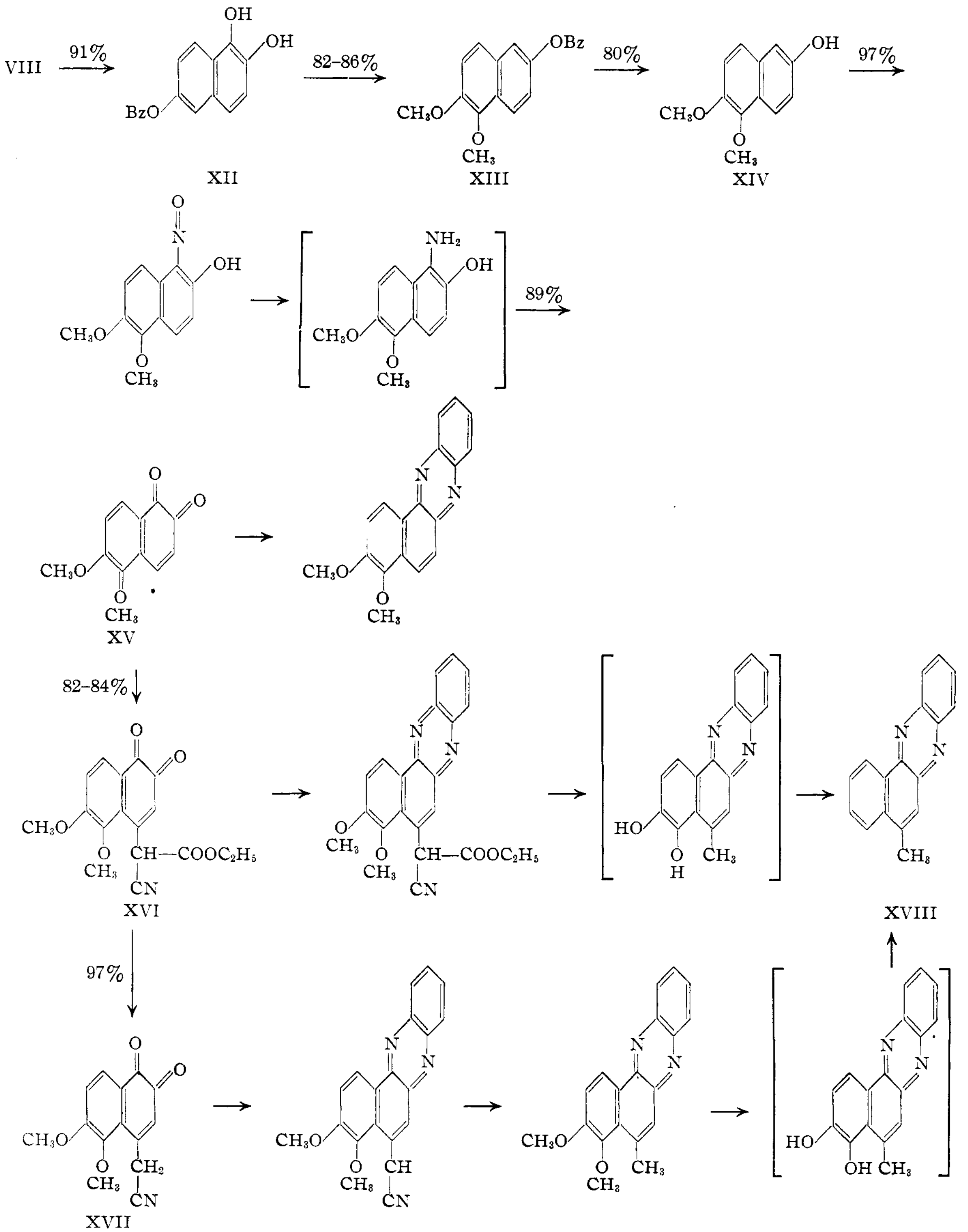
[1] Gates and Newhall, THIS JOURNAL, **70**, 2261 (1948); *Experientia*, **5**, 285 (1949).

[2] *In the first two papers of this series, the structure of the adduct of 4-cyanomethyl-1,2-naphthoquinone and butadiene was formulated as a diketone, but its properties are in better accord with the enolic tautomer I.*

[3] Willstätter and Parnas, *Ber.*, **40**, 1410 (1907).



Craven's test,[4] and a preparative modification of the reaction involved in this test has been worked out which affords ethyl (5,6-dimethoxy-1,2-naphthoquinonyl-4)-cyanoacetate (XVI) in 82–84% yield. The essential feature of this reaction is the base catalyzed condensation of XV and cyanoacetic ester with the addition of ferricyanide ion to reoxidize the by-product 5,6-dimethoxy-1,2-naphthohydroquinone.

The cyanoacetic ester condensation product XVI is rapidly and quantitatively cleaved by

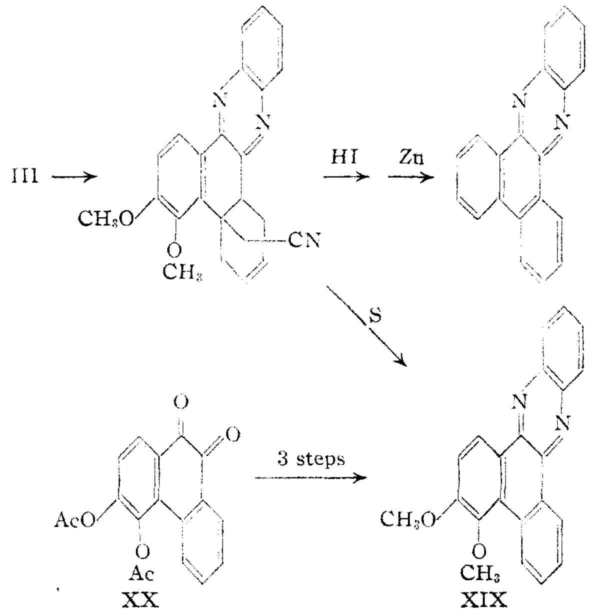
[4] Craven, *J. Chem. Soc.*, 1605 (1931).

Claisen's alkali at room temperature to yield 5,6 - dimethoxy - 4 - cyanomethyl - 1,2 - naphthoquinone (XVII).

It was possible to demonstrate rigidly that nitrosation of XIV occurs in the 1 position and that the quinones XV, XVI and XVII are 1,2-naphthoquinones and also that the cyanoacetic ester residue of XVI and the cyanomethyl residue of XVII occupy the 4 position by converting both XVI and XVII through their respective azines to 5-methylbenzo[a]-phenazine (XVIII) by cleavage, hydrolysis and decarboxylation with acids followed by zinc dust distillation.

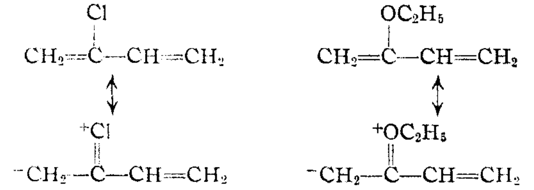
The synthetic steps and structure proofs described above are summarized in the diagram.

The quinone XVII, like the parent unsubstituted quinone,[1] condenses with dienes to give crystalline colorless adducts, soluble in alkali. The addition of butadiene to XVII to give the adduct III in 50% yield has been shown to occur at positions 3 and 4 of XVII by the conversion of the azine of III to both phenanthrenequinoneazine and to the previously unknown[5] azine of 3,4-dimethoxyphenanthrenequinone (XIX).



The azine XIX was also prepared for purposes of comparison by an unambiguous alternative route starting with morpholquinone diacetate (XX)[6] which was converted to its azine, hydrolyzed and methylated.

The dienes chloroprene and 2-ethoxybutadiene also condense with XVII, although yields are poor and the product in the case of 2-ethoxybutadiene has not been fully characterized. Like the other adducts of this series, these substances are colorless crystalline solids soluble in alkali. The structures IV and V have been provisionally assigned to them. The choice of position 6 for the substituent (–Cl or –OC_2H_5) follows from a consideration of the forms XXI and XXII, both of which suggest higher electron density on the end of the diene nearer the substituent. The orientations shown in IV and V would thus result from the interaction of XXI and XXII with XVII, in which position 4 is electron deficient.[7]



Experiments directed toward the reduction and ring closure at position 9 of the adducts III, IV and V are in progress.

We wish gratefully to acknowledge the help of a Frederick Gardner Cottrell Special Grant-in-aid from the Research Corporation with which a large part of the expenses of this work have been defrayed. Our especial thanks are due Dr. R. I. Baker of the Grasselli Plant, General Aniline Works, who very generously undertook the preparation of a substantial quantity of 2,6-dihydroxynaphthalene from Schaeffer's acid for us. We are also indebted to the E. I. du Pont de Nemours Company for a generous sample of chloroprene. Finally, it is a pleasure to acknowledge the efficient and devoted help in a part of the preparative work of Miss Ethelwyn Clark, Miss Cristel Kappes and Miss Rosemarie Künzli.

Experimental Part[8]

2,6-Dihydroxynaphthalene Monobenzoate (VI).[9]—In a 1-l. flask set up over a steam-bath and fitted with a sealed stirrer, 50 g. of 2,6-dihydroxynaphthalene was dissolved by heating and stirring in 300 cc. of purified dioxane (refluxed and distilled over sodium). Distilled benzoyl chloride (100 cc.) was added, followed immediately by 22 cc. of pyridine ("refined" grade). The mixture, which separated into two phases, was stirred vigorously with steam heating for three hours.

At the end of this period the reaction mixture was poured into 5 liters of cold water and stirred until the precipitated solid had thoroughly agglomerated. The precipitate, washed thoroughly with water and dried, consists largely of 2,6-dihydroxynaphthalene mono and dibenzoates together with adsorbed benzoyl chloride.

Separation of the mono and dibenzoates was achieved by making use of the extreme insolubility of the dibenzoate in alcohol (20 cc. of boiling absolute alcohol dissolves only

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[5] E. Vongerichten (*Ber.*, **33**, 1825 (1900)) briefly described the oxidation of 3,4-dimethoxyphenanthrene to a quinone and the condensation of this quinone with *o*-phenylenediamine, but both products were oils and neither was analyzed.

[6] We were saved much effort by Professor Louis F. Fieser who generously supplied us with a sample of this substance.

[7] The condensation of 2-ethoxybutadiene and acrolein, which results in 4-ethoxy-1,2,3,6-tetrahydrobenzaldehyde, proceeds according to a similar orientation; *cf.* A. A. Petrov, *J. Gen. Chem.* (*U. S. S. R.*), **11**, 661 (1941). The work of Holmes, THIS JOURNAL, **69**, 2000 (1947), also supports the orientation chosen above.

[8] All melting points are corrected, unless otherwise designated. All samples for analysis, unless otherwise specified, were dried at 78° and 10^{-4} mm.

[9] The procedure for this preparation was worked out by Miss Rosemarie Künzli.

34 mg. of the dibenzoate. In contrast the monobenzoate is very readily soluble.) The crude mixture was refluxed for five minutes, with 300 cc. of alcohol, filtered, and the colorless insoluble dibenzoate was washed with additional alcohol (28 g. (25%), m. p. 211–215°). A small sample was recrystallized several times from benzene for analysis, colorless plates, m. p. 219.5–220.5°.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.25; H, 4.38. Found: C, 78.69; H, 4.61.

The dibenzoate is not immediately soluble in, but is rapidly hydrolyzed by, aqueous alkalies. If the alkaline solutions are protected from air, good quality 2,6-dihydroxynaphthalene can be recovered on carbonation.

Crystalline monobenzoate VI was recovered from the alcoholic filtrate by strong dilution with water containing sodium bicarbonate, 58 g. (71%), oven dried, m. p. 188–191°. If crude 2,6-dihydroxynaphthalene has been used, the product may melt as low as 182–185°, but may be purified by crystallization from benzene containing a small amount of acetone. A small sample was recrystallized for analysis, colorless plates or leaves, m. p. 192.5–193.5°.

Anal. Calcd. for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58. Found: C, 77.22; H, 4.70.

It is soluble in aqueous alkalies, the solutions rapidly acquiring a brown color in air.

6-Benzoyloxy-1-nitroso-2-naphthol (VII).—Finely ground 6-benzoyloxy-2-naphthol (40 g.) was suspended in a mixture of 400 cc. of acetic acid and 80 cc. of water externally cooled by an ice-bath and 11 g. of solid sodium nitrite was added all at once. An additional 0.5 g. of sodium nitrite was added after ten minutes. The mixture was stirred for two hours and the bright yellow-ocher precipitate was collected, washed with aqueous acetic acid, and slurried with methanol, to yield 39.3 g. (88.5%) m. p. 152–153.5° with profound decomposition. The substance cannot be recrystallized under ordinary conditions without decomposition. For analysis, a small sample was slurried with methanol twice and dried under vacuum, m. p. 154.5–155° with decomposition. It is very sparingly soluble in methanol, rather insoluble in acetic acid. It dissolves in concentrated sulfuric acid with a deep brown color.

Anal. Calcd. for $C_{17}H_{11}NO_4$: C, 69.62; H, 3.78. Found: C, 70.13; H, 4.01.

Dilution of the acetic acid filtrates with water yielded 2.4 g. of much poorer quality nitroso compound, m. p. 105–115°, with decomposition, which, however, could be converted to good quality 6-benzoyloxy-1,2-naphthoquinone in 40–50% yield. If the original monobenzoate has been insufficiently ground, dilution of the methanolic filtrate may yield as much as several grams of impure 6-benzoyloxy-2-naphthol, m. p. 177–184°.

6-Benzoyloxy-1,2-naphthoquinone, VIII.—6-Benzoyloxy-1-nitroso-2-naphthol (20 g.) suspended in 600 cc. of 65% acetic acid was reduced catalytically over 3 g. of prereduced 5% palladium-carbon. During forty-five minutes, 95% of the theoretical amount of hydrogen for 2 moles was absorbed. The hydrogenation flask was flushed with nitrogen and the catalyst was removed by vacuum filtration into a nitrogen-flushed flask. The clear golden-yellow filtrate was oxidized immediately by a solution of 37.4 g. of ferric chloride hexahydrate in 1160 cc. of water and 40 cc. 12 *N* hydrochloric acid, added all at once with swirling. The golden-yellow quinone precipitated immediately, 16.6 g. (87.5%), m. p. 152–154.5° with decomposition. Occasional samples melt as high as 156°. The quinone cannot be recrystallized without decomposition, but is analytically pure as obtained by this procedure. For analysis a sample was dried at 10^{-4} mm.

Anal. Calcd. for $C_{17}H_{10}O_4$: C, 73.38; H, 3.62. Found: C, 73.32; H, 3.70.

It dissolves in concentrated sulfuric acid with the production of a beautiful purple color preceded by a very transient green. Its **azine (IX)** was prepared by refluxing for two minutes 500 mg. of the quinone, 194 mg. of *o*-phenylenediamine, 20 cc. of alcohol and 1 cc. of 12 *N* hydrochloric acid. The precipitated solid was collected, washed with alcohol and dried, 430 mg., m. p. 171–175°. It was purified for analysis by sublimation and several crystallizations from pyridine, m. p. 177.3–178.1°. Its solution in concentrated sulfuric acid is deep reddish purple.

Anal. Calcd. for $C_{23}H_{14}O_2N_2$: C, 78.84; H, 4.03; N, 8.00. Found: C, 78.53; H, 4.20; N, 8.42.

Hydrolysis of the above azine (44 mg.) by short boiling in aqueous methanolic potassium hydroxide yielded **3-hydroxybenzo[a]phenazine (X)**, which was obtained (31 mg. yellow solid, m. p. 286–288° uncor.) by acidification of the alkaline solution with dilute acetic acid. It was dried and analyzed without further purification.

Anal. Calcd. for $C_{16}H_{10}ON_2$: C, 78.03; H, 4.09. Found: C, 77.79; H, 4.62.

The free hydroxy azine dissolves in aqueous alkalies with an orange color. Its solution in concentrated sulfuric acid is a beautiful deep purple. Zinc dust distillation of the free hydroxy compound (24 mg.) from 270–500° yielded a sublimate (1.6 mg. of pale yellow needles, m. p. 130–135°) which after filtration and three crystallizations from methanol melted at 138.5–139.5°. Its mixed m. p. with authentic benzo[a]phenazine (XI)[10] of m. p. 140.5–141.5°, prepared from β-naphthoquinone, was 139.5–140.5°.

6-Benzoyloxy-1,2-naphthohydroquinone (XII).—6-Benzoyloxy-1,2-naphthoquinone (20.0 g.) was suspended in a mixture of 40 cc. of water and 130 cc. of methanol which had been previously treated with sulfur dioxide. Sulfur dioxide was bubbled in slowly with swirling and water cooling for about thirty minutes. The quinone slowly went into solution to yield a deep purple-brown solution which lightened to yellow green on the addition of 1 g. of hydrosulfite. The solution was filtered with Norite and a diatomaceous filter aid, and the hydroquinone was precipitated from the filtrate by careful dilution to about 800 cc. with water, 18.3 g. (91%) oven-dried, m. p. 208–210° with decomposition. A small sample was recrystallized three times from dilute methanol containing sulfur dioxide for analysis; pale tan very small prismatic needles, m. p. 212–214° with decomposition and softening from 209°. It is sparingly soluble in benzene, readily soluble in methanol.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.58; H, 4.57.

It dissolves in concentrated sulfuric acid with a pale olive-green color.

5,6-Dimethoxy-2-naphthol Benzoate (XIII).—In a 500-cc. flask fitted with a nitrogen inlet tube, a sealed stirrer and a calcium chloride tube 60 g. of anhydrous potassium carbonate and 4 g. of sodium hydrosulfite were suspended in 200 cc. of acetone. The flask was flushed with nitrogen, a slight positive pressure of nitrogen was maintained and 20.0 g. of 6-benzoyloxy-1,2-naphthohydroquinone was introduced, followed by 25 cc. of dimethyl sulfate. After stirring for three hours under nitrogen, the mixture was transferred to a beaker and diluted to about 700 cc. with water. The precipitated light yellow solid was washed well with water, slurried with 100 cc. of methanol, and washed with methanol, 18–19 g. (82–86%), m. p. 137–139.5°. For analysis, a small sample was recrystallized several times from methanol-benzene, colorless prismatic leaves, m. p. 140.5–142°. It is fairly soluble in hot benzene, rather sparingly soluble in hot methanol. It dissolves in concentrated sulfuric acid with a bright yellow-green color which rapidly changes to emerald green. This procedure has been used with runs as large as 70 g.

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23; OCH_3, 20.13. Found: C, 74.24; H, 5.38; OCH_3, 19.24.

5,6-Dimethoxy-2-naphthol (XIV).—In a 1-liter flask 20.0 g. of 5,6-dimethoxy-2-naphthol benzoate was suspended in a solution of 16 g. of potassium hydroxide and 1 g. of sodium hydrosulfite in 40 cc. of water and 80 cc. of methanol. The flask was flushed with nitrogen, the liquid heated

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[10] O. Witt, *Ber.*, **20**, 574 (1887).

to boiling, diluted immediately with 500 cc. of water, and the clear solution was carbonated to excess. The product precipitated as a pale yellow to grey crystalline solid. Material obtained in this way is hydrated, and melts unsharply from about 100 to 125° with gas evolution. It was dried in the steam oven, 11.5 g. (87% crude), m. p. 120–124°. The dried material was purified by distillation under high vacuum through a wide side arm all-glass apparatus, bath temperature 180–220°. The nearly colorless distillate which solidified immediately was removed from the receiver with boiling benzene and crystallized from benzene, concentrating the solution until spontaneous crystallization set in, to yield 10.6 g. of heavy nearly colorless prisms, m. p. 131–133° (80.4%). 5,6-Dimethoxy-2-naphthol is occasionally obtained in a polymorphic modification, m. p. 125–126.5°. If this form is melted and allowed to resolidify, it then exhibits m. p. 131–133°. A sample was recrystallized from benzene several times for analysis: heavy colorless prisms, m. p. 131.5–133°. It dissolves in concentrated sulfuric acid with a yellow-green to emerald-green color.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.86; H, 5.98.

5,6-Dimethoxy-1-nitroso-2-naphthol.—Twenty grams of 5,6-dimethoxy-2-naphthol was dissolved in 80 cc. of glacial acetic acid by warming. The solution was cooled rapidly to room temperature in an ice-bath and 220 g. of ice and water were added. The temperature fell rapidly to −10°, and the creamy, finely divided naphthol suspension was treated with 6.90 g. of solid sodium nitrite added all at once. Gentle swirling was continued for ten minutes during which the nitroso compound separated and the naphthol went into solution. At the end of this time an additional 0.8 g. of sodium nitrite was added. After swirling for fifteen more minutes, the bright ocher-colored solid was collected, washed with a little ice-cold 45% acetic acid, then with water, and dried in air; 22.1 g. (97%) m. p. 173–175° with profound decomposition. The substance cannot be recrystallized without decomposition. It was dried and analyzed without further purification.

Anal. Calcd. for $C_{12}H_{11}O_4N$: C, 61.80; H, 4.76. Found: C, 61.46; H, 4.93.

It is soluble in dilute alkalies with a brown color which is yellow-green in thin layers. Its solution in concentrated sulfuric acid is deep greenish-blue.

5,6-Dimethoxy-1,2-naphthoquinone (XV).—To a suspension of 2 g. of pre-reduced palladium on carbon catalyst (5%) in 250 cc. of water, 75 cc. of acetic acid and 5 cc. of 6 *M* sulfuric acid was added 10 g. of 5,6-dimethoxy-1-nitroso-2-naphthol. The mixture was shaken under hydrogen at approximately one atmosphere until the theoretical amount of hydrogen (2 moles) had been absorbed (less than one hour usually). The hydrogenation flask was opened, flushed with nitrogen and its contents filtered by suction into a nitrogen-flushed filter flask. The flask and funnel were washed with a little 3–5% sulfuric acid, and the pale yellow filtrate was oxidized immediately with a solution of ferric chloride hexahydrate (28 g.) in 380 cc. of water and 20 cc. of concentrated hydrochloric acid, added all at once with vigorous swirling. After a few seconds the deep brown solution suddenly began to deposit fine bright golden-yellow needles. Oven dried, the product weighed 8.33 g., yield 89%, m. p. 170–172°. Material prepared in this way is analytically pure.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.98; H, 4.84.

Attempts to carry out this reaction on a larger scale than that described were unsuccessful.

The quinone gives a positive Craven test[3] and dissolves in concentrated sulfuric acid with a beautiful deep carmine to red-purple color which becomes brown on dilution with water. Its **azine** was prepared by treating 100 mg. of the quinone and 50 mg. of *o*-phenylenediamine with 5 cc. of alcohol and 1 cc. of 12 *M* hydrochloric acid. The red needles of the hydrochloride were collected after diluting with 10 cc. of water at the end of five minutes, and converted to the free azine by treatment with alcohol–pyridine. Two recrystallizations from alcohol–pyridine yielded 98 mg. of beautiful long fine pale yellow needles, m. p. 173.5–174.4°. Its solution in concentrated sulfuric acid is a deep ultramarine blue.

Anal. Calcd. for $C_{18}H_{14}O_2N_2$: C, 74.47; H, 4.86. Found: C, 74.79; H, 5.34.

Ethyl (5,6-Dimethoxy-1,2-naphthoquinonyl-4)-cyanoacetate (XVI).—5,6-Dimethoxy-1,2-naphthoquinone (10.0 g.) was suspended in a mixture of 340 cc. of alcohol and 6.8 cc. of ethyl cyanoacetate and treated with 14 cc. of triethylamine. A deep purple color was produced immediately and the suspended golden-yellow quinone went into solution rapidly. The solution was swirled for four minutes, treated with a solution of 30.5 g. of potassium ferricyanide in 100 cc. of water, and swirled for seven more minutes. On the addition of the oxidant, a transient precipitate of 5,6-dimethoxy-1,2-naphthoquinone may be noticed. A solution of 8 g. of sodium carbonate in 800 cc. of water was then added, and the deep purple solution was filtered and acidified all at once while stirring with 100 cc. of 6 *M* sulfuric acid. The initially light yellow precipitate rapidly turned dark orange. After short standing, it was washed thoroughly with water, then slurried with alcohol and finally washed twice with minimal portions of alcohol. The alcohol removes a dark tarry impurity completely, leaving the product as a light orange powder, 12.7 g., oven dried (84%), m. p. 212.5–214°. It contains a trace of complex iron salts, but can be used without further purification. For analysis, a small sample was crystallized several times from ethyl acetate, clear orange prisms or prismatic needles, m. p. 218–219°.

Anal. Calcd. for $C_{17}H_{15}O_6N$: C, 62.00; H, 4.59. Found: C, 62.02; H, 4.77.

It is sparingly soluble even in boiling benzene or methanol, fairly soluble in hot chloroform or ethyl acetate. It dissolves readily in dilute alkalies or alkali carbonates to give deep purple solutions. Its solution in concentrated sulfuric acid is deep gray-black, but viewed in thin layers by transmitted light is deep red. Its pale yellow **azine**, prepared in alcoholic hydrochloric acid and crystallized several times from alcohol–pyridine, has m. p. 187–188°.

Anal. Calcd. for $C_{23}H_{19}O_4N_3$: C, 68.82; H, 4.77. Found: C, 69.08; H, 5.01.

The azine is sparingly soluble even in boiling alcohol, somewhat soluble in boiling benzene, quite soluble in pyridine. It dissolves with a rose-red color in dilute aqueous alcoholic alkali. Its solution in concentrated sulfuric acid is a brilliant blue.

On refluxing the azine (420 mg.) with 48% hydrobromic acid for six hours, during which the original deep carmine solution turned black and deposited a black solid, and distilling the washed and dried black solid (350 mg.) with zinc dust in a micro-sublimer from 340 to 540°, a viscous brown oil (25 mg.) smelling of heterocyclic bases was obtained. This oil, in benzene, was chromatographed on activated alumina and the weakly adsorbed portion which passed rapidly into the filtrate was washed neutral with dilute alkali and acid, dried, and concentrated to dryness, yielding about 4.5 mg. of yellow oil which solidified on trituration with methanol, m. p. 140–158°. A number of crystallizations from alcohol and from benzene–hexane yielded pale yellow needles of 5-methylbenzo[a]phenazine (XVIII), m. p. 170–172°, whose mixed m. p. with an authentic sample[11] of m. p. 173–174° was 170–172.5°.

5,6-Dimethoxy-4-cyanomethyl-1,2-naphthoquinone (XVII).—Twenty grams of cyanoacetic ester condensation product XVI was added to 200 cc. of Claisen alkali maintained at 25–30° and swirled for four minutes, during which the color changed from deep purple to a deep crimson red with no bluish tinge. At the end of four minutes 20 cc. of methanol was added to dissolve a small amount of gummy potassium salt, the solution was swirled one more minute and then acidified all at once with an ice-cold mixture of

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[11] Fieser and Bradsher, THIS JOURNAL, **61**, 417 (1939).

230 cc. of 6 *N* hydrochloric acid and 80 cc. of water. The dirty orange precipitate after short standing was washed thoroughly with water, slurried with methanol, and finally washed once or twice with methanol. Oven dried, the light orange material weighed 15.2 g. (97%), m. p. 227–229.5° with decomposition. A small sample was recrystallized several times from acetic acid for analysis, bright golden-yellow fine needles, m. p. 227–229.5° with decomposition.

Anal. Calcd. for $C_{14}H_{11}O_4N$: C, 65.36; H, 4.31. Found: C, 65.31; H, 4.43.

It is sparingly soluble in benzene and alcohol, moderately soluble in hot acetic acid and soluble in acetone. It dissolves readily in either dilute alkalies or alkali carbonates to give deep crimson solutions. Its solution in concentrated sulfuric acid is a beautiful deep carmine color. Its **azine**, formed from the quinone and a slight excess of *o*-phenylenediamine in refluxing acetic acid, melts, after several recrystallizations from benzene, at 219–220°, yellow to yellow-green needles. It dissolves in concentrated sulfuric acid with a brilliant cobalt blue color.

Anal. Calcd. for $C_{20}H_{15}O_2N_3$: C, 72.93; H, 4.59. Found: C, 73.20; H, 4.93.

The azine (440 mg.) on refluxing for thirteen hours in a mixture of 15 cc. of glacial acetic acid, 2 cc. of concentrated sulfuric acid and 2 cc. of water, yields after dilution and neutralization, crude **3,4-dimethoxy-5-methylbenzo[a]phenazine**[12] (374 mg.), m. p. 141–144°, which after sublimation and several crystallizations from alcohol-benzene melted at 152–153° (245 mg.).

Anal. Calcd. for $C_{19}H_{16}O_2N_2$: C, 74.98; H, 5.30; OCH_3, 20.39. Found: C, 74.58; H, 5.49; OCH_3, 20.02.

The ball of tarry material resulting from dilution of the above Zeisel run (a large sample, 55 mg., was purposely taken) with bisulfite solution was distilled with zinc dust in a micro sublimer. From 360 to 380° a yellow crystalline sublimate appeared on the cold finger, and was taken off in benzene. Concentrated and pumped out it weighed 5.7 mg., m. p. 158–163°. Four crystallizations from 60–70° petroleum ether yielded 1.2 mg. of **5-methylbenzo[a]phenazine (XVIII)** as fine pale yellow needles, m. p. 172–173.5°, mixed m. p. with an authentic sample[11] of m. p. 172.5–174°, 172.5–174°. Both samples give the same deep brown-purple color on solution in concentrated sulfuric acid.

3,4-Dimethoxy-9,10-dioxo-13-cyanomethyl-5,8,9,10,-13,14-hexahydrophenanthrene (III).—5,6-Dimethoxy-4-cyanomethyl-1,2-naphthoquinone (3.00 g.), 20 cc. of butadiene and 30 cc. of glacial acetic acid were heated in a pressure bottle for forty-eight hours at 85–87°. After cooling and opening the bottle, its contents were transferred to a beaker and concentrated by a directing current of air toward the surface. Pale yellow-green prisms began to separate from the very dark solution almost at once. After standing a day, this crop was collected, 1.71 g., m. p. 237–238.5°. A second crop, once recrystallized from benzene–methanol, gave an additional 0.10 g., m. p. 237–238°, total yield 50%. A small sample was recrystallized several times from benzene for analysis, nearly colorless prisms or prismatic blades, m. p. 238–239° without decomposition.

Anal. Calcd. for $C_{18}H_{17}O_4N$: C, 69.44; H, 5.51. Found: C, 69.77; H, 5.65.

The adduct is rather sparingly soluble in methanol and benzene. It dissolves readily in dilute aqueous alkalies with the production of a pale yellow color, and can be recovered unchanged from this solution by acidification. It is decomposed by heating in alkaline solution. Its solution in concentrated sulfuric acid is bright orange-yellow. Its nearly colorless or very pale yellow **azine** is produced in high yield by refluxing the adduct with somewhat more than the theoretical amount of *o*-phenylenediamine in glacial acetic acid for four hours. It crystallizes from benzene–alcohol as faintly yellow platelets, m. p. 225–226°.

Anal. Calcd. for $C_{24}H_{21}O_2N_3$: C, 75.17; H, 5.52; OCH_3, 16.19. Found: C, 75.41; H, 5.75; OCH_3, 15.94.

The azine is sparingly soluble in alcohol, insoluble in dilute alkali, and dissolves in concentrated sulfuric acid with a deep amethyst-purple color. On dilution with water the sulfuric acid solution turns bright yellow and deposits an orange crystalline precipitate. A sample of the azine (491 mg.) was refluxed for twenty minutes with colorless hydriodic acid, d. 1.7, in a carbon dioxide atmosphere, and the material which precipitated on dilution with bisulfite solution was dried and distilled with zinc dust in a microsublimer. From 470 to 520° a tarry distillate, partially solid, appeared on the cold finger. It was taken into benzene, washed neutral, and concentrated to dryness, yielding 27 mg. of gummy brown solid, which by chromatographing in benzene on freshly activated alumina, was separated into a pale yellow very weakly adsorbed fraction which passed readily into the filtrate, and several strongly adsorbed fractions. The weakly adsorbed fraction was concentrated to yield about 1 mg. of yellow crystalline material, m. p. 190–205°, which after four recrystallizations from 60–70° petroleum ether consisted of very pale yellow fine needles, m. p. 217–221°, whose mixed m. p. with authentic phenanthrenequinoneazine[13] of m. p. 224–225° was 219–222°. Its solution in concentrated sulfuric acid was a delicate peach-pink color, indistinguishable from that of phenanthrenequinoneazine.

Dehydrogenation of the azine (1.08 g.) by means of sulfur (190 mg.) was carried out by heating at 250–280° for forty minutes. The black residue was extracted three times with boiling acetic acid, and the extract, after removal of the acetic acid by concentration, was sublimed twice at 10^{-4} mm. to yield 201 mg. of deep orange-red gummy solid. On chromatographing this material in benzene on freshly activated alumina, most of it remained on the column in the form of several strongly adsorbed bands, but a small amount of weakly adsorbed pale yellow material passed readily into the filtrate, which on concentration yielded 11.6 mg. of yellow solid, m. p. 193–202°. After many crystallizations from benzene–hexane, methanol, and acetic acid this substance melted somewhat unsharply at 209–211° and consisted of small bright yellow blades. It still contained a stubborn impurity, but on mixture with an authentic sample of 3,4-dimethoxyphenanthrenequinoneazine of m. p. 217–218° it melted at 211–214°. Its solution in concentrated sulfuric acid was a beautiful deep blue-purple indistinguishable from that exhibited by 3,4-dimethoxyphenanthrenequinoneazine in sulfuric acid.

The comparison sample of 3,4-dimethoxyphenanthrenequinoneazine was prepared as follows: Diacetylmorpholquinone[6] (44 mg.), 15 mg. of *o*-phenylenediamine and 0.5 cc. of glacial acetic acid were refluxed for fifteen minutes, enough more acetic acid was added to effect solution of the pale yellow product, and the mixture was allowed to crystallize. The **3,4-diacetoxyphenanthrenequinoneazine** so obtained, 41 mg., pale yellow solid, m. p. 235–236.5°, was analyzed without further purification. It dissolves in concentrated sulfuric acid with a deep red-purple color which very quickly changes to indigo-blue-black. On dilution with water, a red-orange solid precipitates.

Anal. Calcd. for $C_{24}H_{16}O_4N_2$: C, 72.72; H, 4.07. Found: C, 72.18; H, 4.38.

The azine (33 mg.) was suspended in methanol, flushed with nitrogen, and treated with dilute alkali containing some hydrosulfite. A transient orange color gave way to grey and then to a deep blue-black. The mixture was heated to 60°, then poured into an excess of acetic acid. The dirty greenish suspension which resulted gave a flocculent indigo-blue precipitate on acidification with hydrochloric acid. On aeration, the indigo-blue precipitate turned orange red. Without further characterization, this precipitate was dissolved in 20 cc. of acetone and

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(12) The ready decarboxylation of 5-benzo[a]phenazinylacetic acids has been observed before in this Laboratory; *cf.* This Journal, **70**, 2261 (1948), citation 3.

(13) O. Hinsberg, *Ann.*, **237**, 340 (1887).

stirred under nitrogen for three hours with 0.5 cc. of dimethyl sulfate and 2 g. of anhydrous potassium carbonate. The mixture became quite dark at the start, but quickly lightened to a pale yellow. At the end of the stirring period the mixture was diluted strongly with water and stirred for fifteen minutes. The pale yellow solid was collected, washed with water, dried and crystallized from glacial acetic acid with the aid of norite, yellow needles mixed with some colorless material, possibly sulfur, 34 mg., m. p. 201–210°. It was recrystallized twice from benzene to give yellow prismatic needles of **3,4-dimethoxyphenanthrenequinoneazine (XIX)**, 20 mg., m. p. 218.5–219°. Its solution in concentrated sulfuric acid is a deep blue-purple color.

Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74. Found: C, 77.38; H, 5.05.

3,4-Dimethoxy-6-chloro-9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (IV).—A mixture of 4.00 g. of XVII, 28 g. of freshly distilled chloroprene, 0.1 g. of hydroquinone and 40 cc. of purified dioxane was heated for four and one-half days at 85–87° in a pressure bottle. The cooled contents of the bottle were washed out with methanol and the whole mixture was concentrated to dryness by a current of air. The non-volatile dark residue consisted of mixed crystalline material and heavy oil. It was triturated with cold methanol and the insoluble solid material was collected, 1.43 g., m. p. 235–240° with preliminary shrinking and softening from 220°. This solid was washed alternately with bicarbonate and water until the filtrates were no longer red to yield 1.20 g. of olive-green crystalline material, m. p. 259–265°. Recrystallization from methanol with the aid of norite yielded 0.89 g. (16.6%) of nearly colorless small prisms, m. p. 265–267°. A small sample was recrystallized once more for analysis, m. p. 267.5–269°.

Anal. Calcd. for $C_{18}H_{16}O_4NCl$: C, 62.52; H, 4.66; Cl, 10.26. Found: C, 62.29; H, 4.74; Cl, 10.86.

The adduct is very sparingly soluble even in boiling methanol, benzene or ethyl acetate. It is somewhat soluble in boiling dioxane. It is soluble in quite dilute aqueous alkalies to give a pale yellow solution but is difficultly soluble in more concentrated alkalies. Its solution in concentrated sulfuric acid is bright orange-yellow. No trace of silver chloride is produced on boiling the adduct in alcoholic silver nitrate for ten minutes.

3,4-Dimethoxy-6-ethoxy-9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (V).—A mixture of 4.00 g. of XVII and 12 g. of 2-ethoxybutadiene was heated for two days at 85–87° in a pressure bottle. The resulting viscous brown tar was taken into benzene and separated into bicarbonate soluble, alkali soluble and neutral fractions. The alkali soluble fraction, 0.52 g., m. p. 100–120°, was dissolved in alcohol and on standing yielded 92 mg. of crystalline material, m. p. 210–225°. After several recrystallizations 32 mg. of very small nearly colorless prisms, m. p. 226–228°, with softening and much decomposition from about 220°, was obtained. The material was still not homogeneous.

Anal. Calcd. for $C_{20}H_{21}O_5N$: C, 67.59; H, 5.96; alkoxyl, 30.14. Found: C, 66.20; H, 6.41; alkoxyl, 27.3.

Summary

The synthesis of 5,6-dimethoxy-4-cyanomethyl-1,2-naphthoquinone and its condensation with several conjugated dienes to yield 3,4-dimethoxy-9,10-dioxo-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene derivatives are reported.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

The Oxidation of β-Carotene

BY N. L. WENDLER,* C. ROSENBLUM AND M. TISHLER†

The high vitamin A activity of β-carotene[1] has often been ascribed[2,3] to the formation of vitamin A in the animal organism through symmetrical fission of the β-carotene molecule at its center position of unsaturation. Experiments designed to duplicate such a degradation *in vitro* by biochemical methods have met with debatable success.[4]

A consideration of the β-carotene structure (I), suggests the attractive hypothesis that the centrally situated 9:10 double bond might well be the most vulnerable position to reagent attack for reasons of its symmetrical and sterically least hindered disposition. Opposed to favorable stereochemical aspects, however, is the supposition that double-bond interaction in an extended system of conjugated double-bonds of this type would be expected to impart maximal single-bond character at the 9:10 position,[5,3] and thus render this center less favorable to electrostatic orientation of the attacking reagent molecule. Furthermore, the large number of controlled oxidation studies[6] on β-carotene which led to the elucidation of its structure, all resulted in cleavages of the β-carotene molecule wherein the fragments isolated were in full possession of an intact 9:10 double bond.[7] Thus, controlled oxidations with chromic acid and lead tetraacetate[8] resulted in initial end-oxidation in the β-ionone ring giving rise to a series of isolable intermediate oxidation products which were further oxidized with accompanying side chain cleavage to β-carotenone-aldehyde (II). Similarly, controlled oxidation with permanganate[9] was

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[1] von Euler, von Euler and Hellstrom, *Biochem. Z.*, **203**, 370 (1928); C. J. Koehn, *Arch. Biochem.*, **17**, 337 (1948).

[2] Woolf and Moore, *Lancet*, **223**, 13 (1932).

[3] Hunter and Williams, *J. Chem. Soc.*, 554 (1945).

[4] Mattson, Mehl and Deuel, *Arch. Biochem.*, **15**, 65 (1947).

[5] Zechmeister, Le Rosen, Polgár and Pauling, THIS JOURNAL, **65**, 1940 (1943).

[6] Reviews in "Carotinoide," by Karrer and Jucker, Verlag Birkhäuser, Basel, 1948, p. 133; "The Chemistry of Natural Coloring Matters," by Mayer and Cook, Reinhold Publishing Corp., New York, N. Y., 1943, p. 28.

[7] It should be emphasized that any interpretation with regard to the major course of these and other oxidations must be considered with caution since the severe limitation is imposed, that an interpretation can be defined only in terms of the products identified which, in general, do not represent the major portion of the β-carotene utilized.

[8] Kuhn and Brockmann, *Ber.*, **65**, 894 (1932); *Ann.*, **516**, 95 (1935).

[9] Karrer and Solmssen, *Helv. Chim. Acta*, **20**, 682 (1937); Karrer, Solmssen and Gugelmann, *ibid.*, p. 1020.