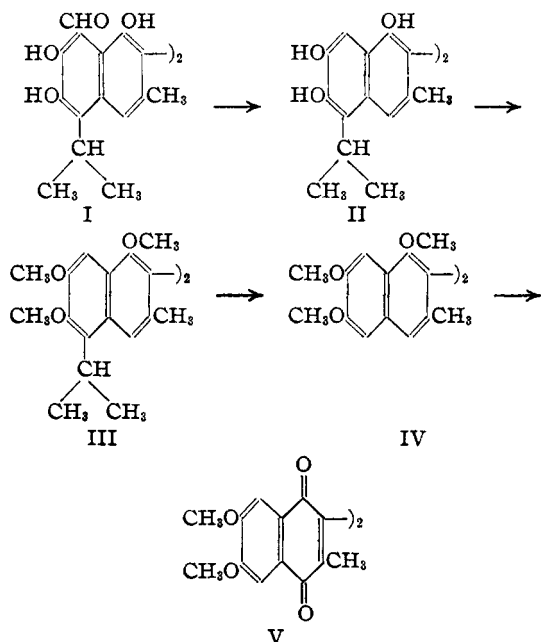


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Gossypol. XXV. Synthesis of Desapogossypolone Tetramethyl Ether¹

BY ROGER ADAMS AND B. R. BAKER

The structure of gossypol was postulated as a binaphthyl derivative (I).² Among some of its important degradation products are apogossypol (II), apogossypol hexamethyl ether (III), desapogossypol tetramethyl ether (IV) and desapogossypolone tetramethyl ether (V).

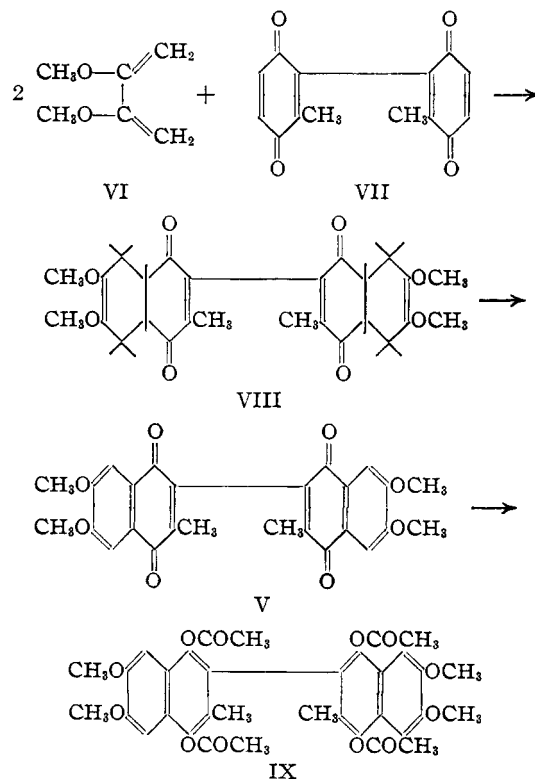


From gossypol, as well as from products II-V, by degradative reactions, there are formed either compounds which contain a binaphthyl residue or substances which are simple benzene derivatives. In no instance was it possible to obtain a substituted naphthalene or a substituted biphenyl. In spite of the fact that absorption spectra, color reactions and the structure of the substituted benzenes all support, in a convincing way, the postulation of a binaphthyl nucleus in gossypol and its lesser degradation products, it was desirable to identify by synthesis one of the binaphthyl compounds. The simplest of these is desapogossypolone tetramethyl ether (V) and was, therefore, selected as probably the most accessible. Several failures to prepare this substance have already been reported.¹

(1) For the two previous papers in this series see Adams, Geissman, Baker and Teeter, *THIS JOURNAL*, **63**, 528 (1941); Adams and Geissman, *ibid.*, **61**, 2083 (1939).

(2) Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, *ibid.*, **60**, 2193 (1938).

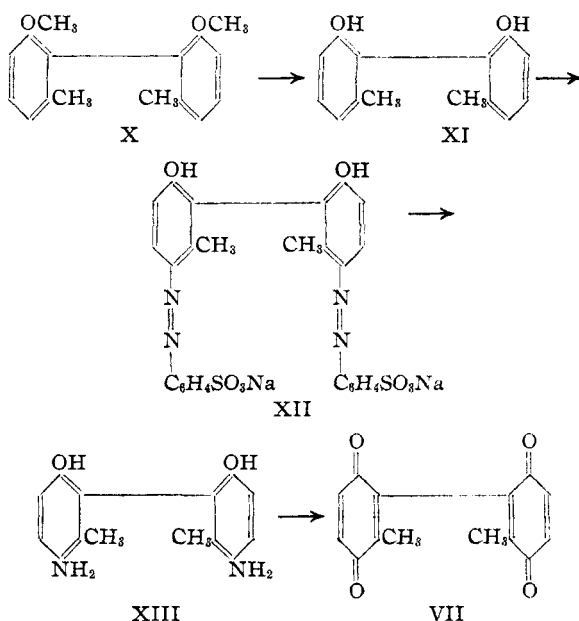
A successful synthesis of this molecule now has been accomplished through the condensation of 2,3-dimethoxybutadiene (VI) with 6,6'-dimethyl-2,5,2',5'-biphenyldiquinone (VII) followed by oxidation of the adduct (VIII) to 2,2'-bi-(3-methyl-6,7-dimethoxy-1,4-naphthoquinone) (V). This last compound proved to be desapogossypolone tetramethyl ether as shown by a mixed melting point of the natural and synthetic products. Both were converted by reductive acetylation to the same compound, 2,2'-bi-(1,4-diacetoxy-3-methyl-6,7-dimethoxynaphthyl) (IX). These experiments serve as the first direct evidence establishing the binaphthyl nucleus in gossypol and thus confirming the indirect evidence.



The synthesis just described does not clarify whether the methyl groups in gossypol (I) hold the position assigned them in relation to the link between the two naphthyls or whether the methyls and the internuclear link should be interchanged.

2,3-Dimethoxybutadiene (VI) was prepared from butadiene by the method of Johnson,

Jobling and Bodamer,³ who have just recently described the synthesis of 2,3-dimethoxy- and 2,3-diethoxybutadiene and their reaction products. 6,6'-Dimethyl-2,5,2',5'-biphenyldiquinone (VII) was synthesized from 2,2'-dimethoxy-6,6'-dimethylbiphenyl (X) by the following series of reactions: (1) demethylation to the corresponding dihydroxy compound (XI), (2) coupling with diazotized sulfanilic acid to the azo compound (XII), (3) reduction to the aminophenol (XIII), and (4) oxidation to the desired quinone (VII).



The addition reaction of 2,3-dimethoxybutadiene to the 6,6'-dimethyl-2,5,2',5'-biphenyldiquinone is complicated by the fact that the adduct VIII is dehydrogenated by means of the unchanged or partially condensed quinone. This was anticipated in view of the observation described by Johnson, Jobling and Bodamer³ in the addition of 2,3-diethoxybutadiene to toluquinone. Actual conditions which proved satisfactory for the 2,3-dimethoxybutadiene and 6,6'-dimethyl-2,5,2',5'-biphenyldiquinone condensation were to employ a very large excess of dimethoxybutadiene and, after the reaction had proceeded, to add chloranil⁴ to the reaction mixture as an oxidizing agent. Extraction of the reaction mixture with alkali, and addition of methanol served to precipitate the crude desapogossypolone tetramethyl ether desired in a yield approximating the weight of the original quinone.

(3) Johnson, Jobling and Bodamer, *THIS JOURNAL*, **63**, 131 (1941).

(4) Arnold, *ibid.*, **61**, 1407 (1939); **62**, 983 (1940).

Experimental

2,2'-Dihydroxy-6,6'-dimethylbiphenyl (XI).—The 2,2'-dimethoxy-6,6'-dimethylbiphenyl was prepared as previously described.⁵ 2-Nitro-3-methoxytoluene was reduced to the corresponding amine with Raney nickel in ethanol in 93% yield. The amine group was replaced by iodine in 80% yield and the coupling reaction resulted in a 70% yield of the desired biphenyl derivative.

A mixture of 24 g. of 2,2'-dimethoxy-6,6'-dimethylbiphenyl, 125 cc. of 48% aqueous hydrobromic acid and 125 cc. of acetic acid was refluxed for three hours. After two hours, the reaction mixture had become homogeneous. Upon dilution to one liter with water the product separated. It was purified by recrystallization from benzene-petroleum ether (b. p. 60–110°); light tan blades, m. p. 160–163° (cor.); yield 16 g. (76%), though in some experiments the yield was considerably better. Varying the ratio of hydrobromic to acetic acid markedly affects the yield. Sugii and Shindo^{6a} reported for this substance m. p. 164° and Sako^{6b} m. p. 161–163.5°.

6,6'-Dimethyl-2,5,2',5'-biphenyldiquinone (VII).—To a solution of 31 g. of sulfanilic acid and 8 g. of anhydrous sodium carbonate in 300 cc. of water, cooled to 15°, was added 10.8 g. of sodium nitrite. The reaction mixture was then poured into 28 cc. of concentrated hydrochloric acid and 150 g. of cracked ice.

This resulting suspension of diazonium salt was introduced into an ice cold solution of 16 g. of 2,2'-dihydroxy-6,6'-dimethylbiphenyl in 180 cc. of water containing 22 g. of sodium hydroxide. After standing for two hours at ice-bath temperature, the deep red solution was warmed on a steam-bath and 48 g. of sodium hydrosulfite added in portions with stirring over a period of about five minutes. The hot solution, which had become yellow, was then saturated with salt. After cooling to 5°, the crude aminophenol was filtered and washed; yield, 14 g. (78%).

The crude dry aminophenol was dissolved in a solution of 52 cc. of concentrated sulfuric acid and 160 cc. of water, and a little insoluble material filtered and washed with a mixture of 52 cc. of concentrated sulfuric acid and 160 cc. of water. The combined filtrate and washing were cooled to 3° in an ice-salt-bath and then was added with swirling a solution of 28 g. of potassium dichromate in 150 cc. of water at such a rate that the temperature did not rise above 3–5°. At the beginning, in order to maintain this temperature, the addition must be very slow. After standing in an ice-bath an hour, the separated product was filtered and washed well with water. The combined filtrate and washings were extracted with two 100-cc. portions of chloroform. The dried precipitate of quinone was dissolved in the chloroform extractions and the solution refluxed for fifteen minutes with Norit. The filtered solution was then evaporated to dryness. The product was recrystallized from ethanol; orange-brown leaflets, m. p. 169–170° (cor.); yield, 9.0 g. (65%).

The substance can be obtained as orange-yellow leaflets with the same melting point by sublimation at 3 mm. (bath temp. 160°) followed by recrystallization from ethanol. The loss in material during these operations is considerable.

(5) Li and Adams, *ibid.*, **57**, 1565 (1935).

(6) (a) Sugii and Shindo, *J. Pharm. Soc., Japan*, **54**, 149 (1934);

(b) Sako, *Bull. Chem. Soc., Japan*, **9**, 55 (1934).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 69.42; H, 4.16. Found: C, 69.68; H, 4.18.

2,2' - Bi - (3 - methyl - 6,7 - dimethoxy - 1,4 - naphthoquinone), (Desapogossypolone Tetramethyl Ether) (V).—A mixture of 27.5 g. of 2,3-dimethoxybutadiene and 2.75 g. of 6,6'-dimethyl-2,5,2',5'-biphenyldiquinone was heated in a loosely stoppered flask on the steam-bath for twenty hours. The excess 2,3-dimethoxybutadiene was recovered by distillation at 30 mm. (bath temp. below 70°). The residue was a viscous gum from which no crystalline material could be obtained. It was dissolved in 40 cc. of xylene, 12 g. of chloranil added and the mixture refluxed for four hours. The black solution was diluted with 100 cc. of benzene and extracted with 100 cc. of 5% aqueous sodium hydroxide. The emulsion which formed was broken by filtration through an asbestos mat. The organic layer was extracted twice more with alkali and then washed with water. The solvent was evaporated from the orange solution and the last traces removed by a stream of air. The gummy residue thus obtained was digested with 30 cc. of warm methanol for fifteen minutes. The gum gradually changed to an orange powder. After cooling, it was filtered (3 g.). The product was purified by two crystallizations from methyl ethyl ketone followed by three from benzene-petroleum ether (b. p. 60–110°); orange prisms, m. p. 251–254° (cor.).

Desapogossypolone tetramethyl ether obtained by degradation of gossypol was reported as melting at 245–248° (uncor.); when corrected this is 251–254° (cor.). A mixture of synthetic and natural specimens gave no depression when melted.

Anal. Calcd. for $C_{26}H_{22}O_8$: C, 67.50; H, 4.76. Found: C, 67.79; H, 4.66.

2,2' - Bi - (1,4 - diacetoxy - 3 - methyl - 6,7 - dimethoxy-naphthyl) (IX).—A mixture of 0.095 g. of pure 2,2'-bi-(3-methyl-6,7-dimethoxy-1,4-naphthoquinone), 0.095 g. of freshly fused sodium acetate, a few tenths of a gram of zinc dust and 2 cc. of acetic anhydride was refluxed for fifteen minutes. The solution was filtered hot and the zinc washed with two 5-cc. portions of acetic acid. The filtrate and washings were poured into water. The product was purified by recrystallization from methanol; white crystals, m. p. 264–265° (uncor.) or 272–273° (cor.). This melting point is identical with that of the substance obtained by similar treatment of natural desapogossypolone tetramethyl ether and a mixed melting point showed no depression.

Anal. Calcd. for $C_{34}H_{34}O_{12}$: C, 64.35; H, 5.36. Found: C, 64.52; H, 5.56.

Summary

The compound 2,2'-bi-(3-methyl-6,7-dimethoxy-1,4-naphthoquinone) has been prepared by condensation of 2,3-dimethoxybutadiene with 6,6'-dimethyl-2,5,2',5'-biphenyldiquinone and oxidation with chloranil of the intermediate adduct. It proved to be identical with desapogossypolone tetramethyl ether obtained from gossypol. The synthetic product on reductive acetylation gave a substance identical with that resulting from a similar treatment of desapogossypolone tetramethyl ether. This synthesis confirms the earlier postulation that gossypol is a binaphthyl derivative.

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Structure of Monocrotaline. VI. The Structure of Retronecine, Platynecine and Retronecanol¹

BY ROGER ADAMS AND E. F. ROGERS

It has been shown that the alkaloid monocrotaline, $C_{16}H_{23}O_6N$, on catalytic hydrogenation, gives retronecanol, $C_8H_{15}ON$, and monocrotalic acid, $C_8H_{12}O_6$. When saponified, the alkaloid, yields retronecine, $C_8H_{13}O_2N$, and the alkaline decomposition products of monocrotalic acid, carbon dioxide and α,β -dimethyllevulinic acid. The two reactions together indicate that monocrotaline is an ester of retronecine in which an hydroxyl group of the alkamine is covered by monocrotalic acid.

In the hydrogenation of monocrotaline, two

moles of hydrogen are absorbed, hydrogenolysis occurs at the ester grouping and the double bond of retronecine is reduced with the formation of the saturated monohydroxy base, retronecanol. A hydrogenation of this type was first observed by Menshikov,² who found that the alkaloid heliotrine, $C_{16}H_{27}O_5N$, which could be saponified to heliotridine, $C_8H_{13}O_2N$ (probably a diastereoisomer of retronecine), and heliotrinic acid, $C_8H_{16}O_4$, gave as reduction products oxyheliotridane, $C_8H_{15}ON$, and heliotrinic acid. Barger³ observed that retrorsine hydrogenates in a similar manner. He found, moreover, that diacetylretronecine reduces to acetylretronecanol and

(1) For previous papers see (a) Adams and Rogers, *THIS JOURNAL*, **61**, 2815 (1939); (b) Adams, Rogers and Sprules, *ibid.*, **61**, 2819 (1939); (c) Adams, Rogers and Long, *ibid.*, **61**, 2822 (1939); (d) Adams and Long, *ibid.*, **62**, 2289 (1940); (e) Adams and Rogers, *ibid.*, **63**, 228 (1941).

(2) Menshikov, *Ber.*, **68**, 1051 (1935).

(3) Barger, Seshadri, Watt and Yabata, *J. Chem. Soc.*, 11 (1935).