

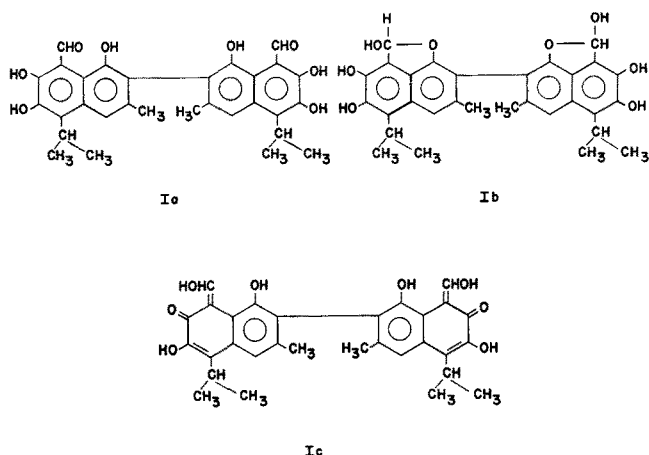
# Synthesis of Gossypol and Gossypol Derivatives<sup>1</sup>

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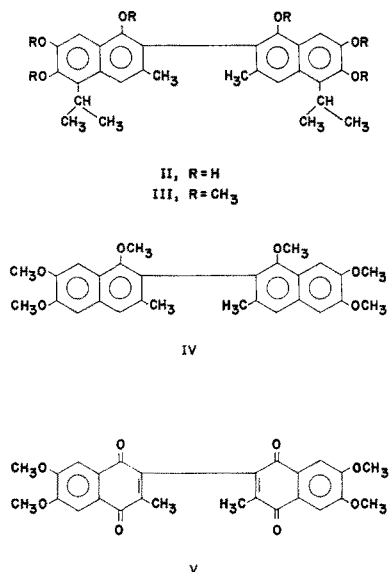
## Abstract

The synthesis of gossypol and certain major degradation products possessing the binaphthyl ring carbon skeleton is discussed.

The structure, 1,1',6,6',7,7'-hexahydroxy-5,5'-diisopropyl-3,3'-dimethyl [2,2'-binaphthalene]-8,8'-dicarboxaldehyde (I), was formulated by Adams et al. (1) for gossypol after their extensive investigations. The three tautomeric forms, Ia, Ib and Ic, were needed to explain all of the reactions and properties of gossypol and its derivatives.

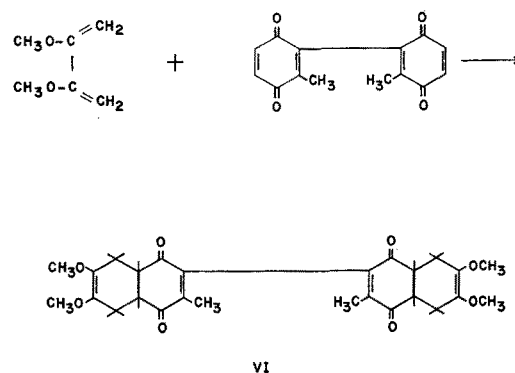


When gossypol is heated in concentrated aqueous sodium hydroxide, the compound apogossypol (II) and two moles of formic acid are formed. Apogossypol is unstable but readily forms a stable hexamethyl ether (III) which reacts with concentrated sulfuric acid at room temperature losing two isopropyl residues to give desapogossypol hexamethyl ether (IV). Oxidation of this hexamethyl ether (IV) gave desapogossypolone tetramethyl ether (V).

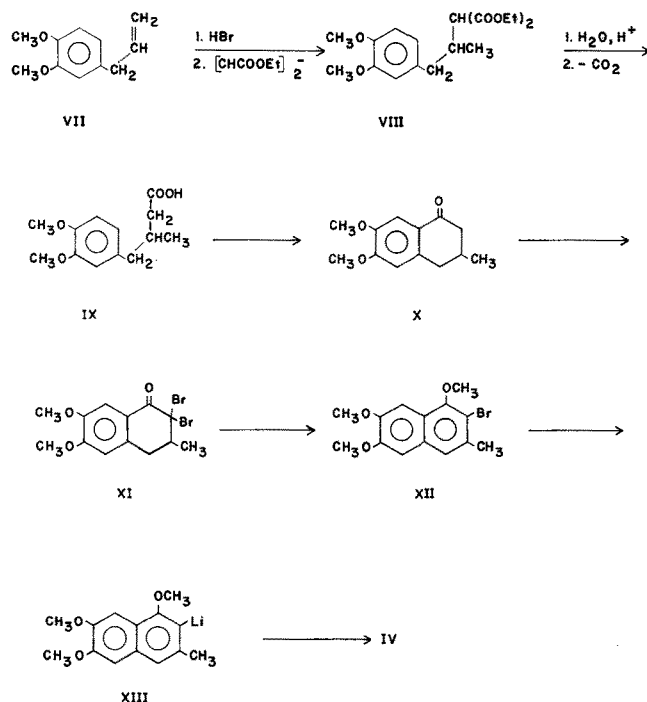


In this paper the synthesis of gossypol and some major degradation products are discussed.

The first synthesis of a degradation product of gossypol containing the binaphthyl ring carbon skeleton was that reported by Adams and Baker (2) for desapogossypolone tetramethyl ether (V). This was accomplished through the Diels-Alder reaction of 2,3-dimethoxy-1,3-butadiene and 6,6'-dimethyl-2,2',5,5'-biphenyldiquinone to give the adduct VI which, on oxidation with chloranil, gave a product identical with desapogossypolone tetramethyl ether (V).



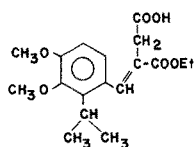
The synthesis in good yield of desapogossypol hexamethyl ether (IV), the precursor of desapogossypolone tetramethyl ether, was reported by Shirley and Dean (4). Their starting material was the methyl ether of eugenol (VII) and this, on addition of hydrogen bromide, gave the corresponding 2-bromopropane derivative which, on condensation with sodiomalonic ester, gave the diester VIII. This product, on hydrolysis and decarboxylation, gave the substituted butyric acid (IX). Ring closure of IX by heating with polyphosphoric acid gave the tetralone X.



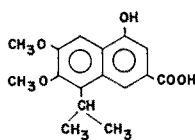
<sup>1</sup> Presented at the Carl M. Lyman Memorial Symposium on Gossypol, AOCS Meeting, New Orleans, April 1970.

The dibromotetralone XI was obtained in quantitative yield from X and the synthesis of 1,6,7-trimethoxy-2-bromo-3-methylnaphthalene (XII) from XI was found to be done best by carrying out the dehydrobromination and methylation in one step using sodium methoxide and dimethyl sulfate in methanol. The bromonaphthalene (XII) on reaction with *n*-butyllithium gave the organolithium compound XIII and this, on treatment with cobalt (II) bromide, coupled and gave a product identical with desapogossypolone tetramethyl ether (IV). Demethylation (4) of IV with pyridine hydrochloride gave desapogossypol.

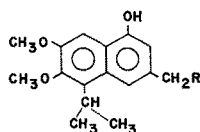
The synthesis of apogossypol hexamethyl ether (III) was achieved (5) by the following series of reactions. The Stobbe condensation of 2-isopropyl-3,4-dimethoxybenzaldehyde and diethyl-succinate gave the expected half-ester XIV and on cyclodehydration with sodium acetate and acetic anhydride followed by



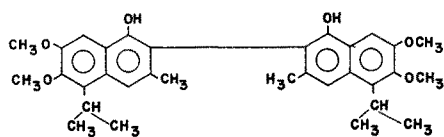
XIV



XV



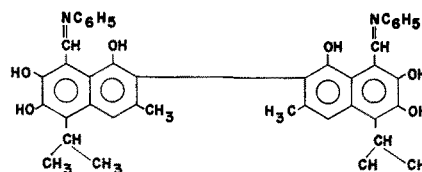
XVI, R = OH  
XVII, R = H



XVIII

saponification this gave the naphthoic acid XV. Reduction of XV with lithium aluminum hydride gave the corresponding hydroxymethyl compound XVI and hydrogenolysis with palladium-on-charcoal formed the naphthol (XVII). This naphthol (XVII) on heating at its melting point, underwent oxidative coupling to form the 2,2'-binaphthol XVIII. Methylation of XVIII gave a product identical with apogossypol hexamethyl ether (III).

The formation of apogossypol (II) from its hexamethyl ether (III) was realized by reaction with an excess of boron tribromide for several hours at room temperature in anhydrous benzene. After evaporation to dryness under vacuum, the borate was hydrolyzed by heating with 30% aqueous potassium hydroxide and upon acidification gave apogossypol (II). The remaining step needed for a total synthesis of gossypol was achieved (6) when it was shown that apogossypol on reaction with *N,N*-diphenylformamidine ( $C_6H_5NHCH=NC_6H_5$ ) gave dianilinogossypol (XIX).



XIX

Since hydrolysis of XIX was known to give gossypol, this completed the synthesis. In a recently published book (7) there is a comprehensive chapter on gossypol and a good list of leading references.

#### REFERENCES

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6. Edwards, Jr., J. D., *Ibid.* **80**, 3798 (1958).
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