cyclic ring is fused to the quinone ring and that the nitrogen is more positive than in the nonthermochromic compounds. Addition of a trace of acid to an aqueous solution of Ib results in a spectrum almost identical with that of a methoxy-substituted quinone; protonation of the nitrogen would have this effect for the structure suggested.

Summary

Both n.m.r. and ultraviolet–visible spectra suggest that the thermochromic aminoquinones consist of a heterocyclic ring fused to the quinone ring, with the nitrogen bearing a partial positive charge. The thermochromic mechanism consists primarily in a decrease of the positive charge on the nitrogen to restore a more usual charge distribution within the quinone ring.

Experimental Section

Spectra were run on a Varian A-60 spectrometer. Temperatures were calibrated by substitution of ethylene glycol into the probe. Frequencies were estimated by taking DMSO-d_5 as 2.52 p.p.m. (151 c.p.s.), compared with TMS. Spectra were run first at the lowest temperature, then the higher temperatures; on cooling down to the lower temperature the original spectra were reproduced unchanged. Absorption spectra were run on a Cary 14 spectrophotometer.

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The Oxidation of Gossypol. II. Formation of Gossypolone with Ferric Chloride

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The oxidation of gossypol (I) with ferric chloride in acetic acid–acetone gave the 1,4-binaphthoquinone II in good yield. Formation of II seemed due to complexation and stabilization of the *o*-hydroxyaldehyde moiety by the ferric chloride and steric blocking of the normal oxidative coupling reaction of phenols.

The 1,4-binaphthoquinone II derived from gossypol (I) has never been prepared although several derivatives were characterized and utilized in the basic work on gossypol structure by Adams and others.[2] Clark[2a] converted gossypol hexaacetate (V) with chromic anhydride to a yellow compound designated by him as tetraacetylgossypolone (Chart I); this experiment was performed prior to knowledge of the structure of gossypol. Clark reported elemental analyses, a molecular weight, and a molecular formula for the product. His molecular formula ($C_{33}H_{30}O_{12}$) does not conform to that for IV ($C_{38}H_{34}O_{14}$), but his elemental analytical data do conform. Later Adams[2b] oxidized gossypol hexamethyl ether with chromic anhydride and obtained tetramethylgossypolone which subsequent work indicated to have the structure VII. Owing to the similar methods of preparation, Adams considered Clark's tetraacetylgossypolone to correspond to IV.[2c]

Mild oxidation of gossypol (I) leads to highly colored products which are probably involved in color fixation in cottonseed oils. We have underway an investigation of the route of oxidative degradation of gossypol under a variety of reaction conditions. In a prior paper[3] we observed the formation of an *o*-binaphthoquinone, 1,1′,6,6′-tetrahydroxy-5,5′-diisopropyl-3,3′-dimethyl-(2,2′-binaphthalene)-7,7′,8,8′-tetraone, from the action of oxygen on gossypol in alkaline solution. We are continuing an investigation of the later stages in this particular oxidative path. The present report deals with the action of ferric chloride in acetic acid–acetone on gossypol. After removal of iron from the initial product, there was obtained in 50–70% yield a quinone of structure corresponding to II. The structure of II is indicated by the n.m.r. spectrum (Table I), infrared spectrum, formation of a tetraacetate derivative (IV), the n.m.r. spectrum of the tetraacetate, and the formation of dianil derivatives III and VI of the quinone and the tetraacetate. The quinone II is 6,6′,7,7′-tetrahydroxy-5,5′-diisopropyl-3,3′-dimethyl-(2,2′-binaphthalene)-1,1′,4,4′-tetraone-8,8′-dicarboxaldehyde but may be designated by the common name "gossypolone" used earlier[2] for derivatives of this substance.

The sample of IV prepared from II was identical with a product made by oxidation of gossypol hexaacetate by the method of Clark.[2a] Both samples of IV melted higher than reported[2a] as did the anil derivatives VI.

Infrared spectra support the structural postulates given above. The carbonyl stretch for gossypol (I) appears at 6.18 μ.[4] Gossypolone (II) shows a band in the carbonyl stretch region which is slightly resolved into two bands appearing at 6.05 and 6.10 μ. These represent the quinone carbonyls and the aldehyde carbonyl, the latter appearing at a somewhat long wave length position owing to the conjugation present. In gossypolone tetraacetate (IV) the aldehyde carbonyl stretch has moved down to 5.85 μ, a normal direction and magnitude of shift for conversion of the hydroxyl group adjacent to carboxaldehyde to an acetoxyl. In addition, the formation of the anil VI caused loss of the 5.85-μ aldehyde carbonyl stretch.

Attempted methylation of II to produce VII was not successful with several different reaction conditions and reagents.

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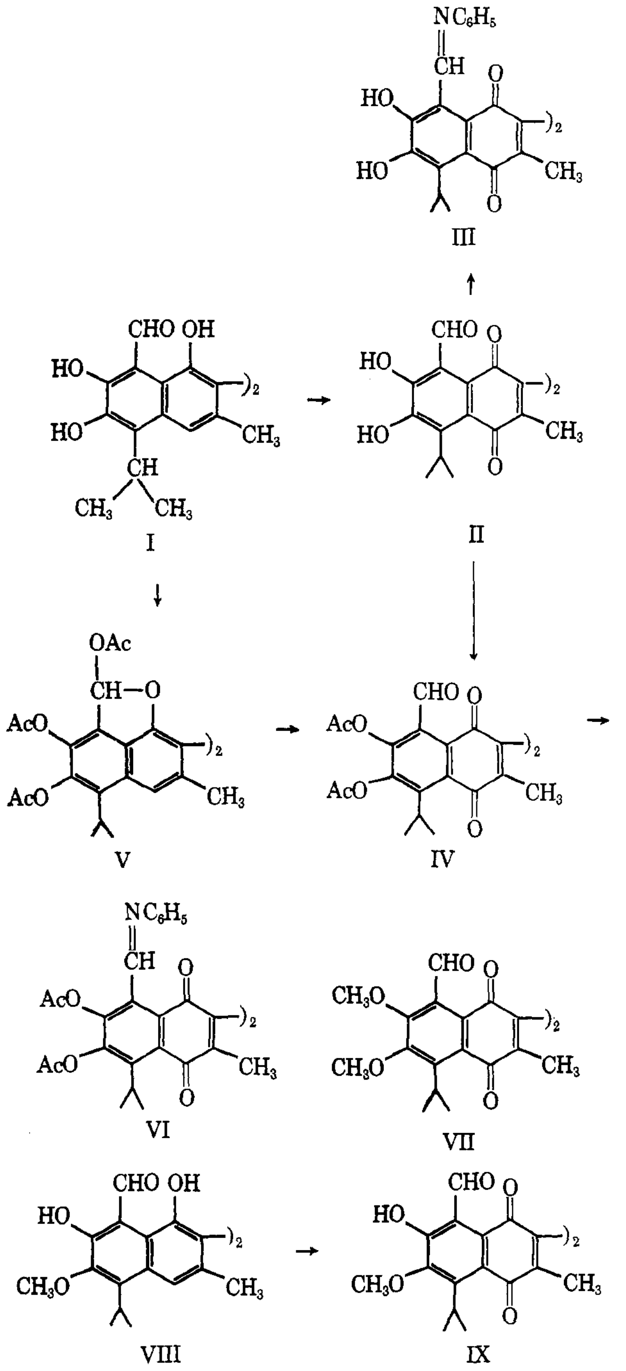
[1] To whom communications concerning this paper should be sent.

[2] (a) E. P. Clark, *J. Am. Chem. Soc.*, **51**, 1475 (1929); (b) R. Adams, R. C. Morris, and E. C. Kirkpatrick, *ibid.*, **60**, 2170 (1938); (c) R. Adams *et al.*, *ibid.*, **60**, 2199 (1938).

[3] E. W. Scheiffele and D. A. Shirley, *J. Org. Chem.*, **29**, 3617 (1964).

[4] R. T. O'Connor, *et al.*, *J. Am. Chem. Soc.*, **76**, 2368 (1954).

CHART I



Adams and Geissman[5] carried out the oxidation of gossypol dimethyl ether (VIII) with ferric chloride to obtain an orange product. The analytical values for carbon and hydrogen were given for the product, but no subsequent structural investigation was reported. It should be pointed out that the reported analytical values check the structure represented by IX, and that this structure is supported by the similarity of reaction conditions to those used for formation of gossypolone and the structural evidence for this latter compound indicated above. We repeated the Adams oxidation of gossypol dimethyl ether[5] and obtained a product of the properties reported by him. The n.m.r. spectrum supports the structure IX as indicated in Table I. The n.m.r. bands for VIII were reported earlier.[3] Changes in the carbonyl stretch region in compounds VIII and IX correspond to those reported above for the gossypol-to-gossypolone conversion.

The conversion of a naphthol to a 1,4-naphthoquinone type with ferric chloride in acetic acid–acetone is apparently an unusual route of quinone formation. It is possible that in gossypol the steric blocking of the position *para* to the 1-hydroxyl group prevents the coupling of two rings, which has been observed in the action of ferric chloride on 1-naphthols. The initial product from the gossypol oxidation is an iron complex of the binaphthoquinone II, and this is likely to involve the iron complexed with the aldehyde group and the adjacent 7-hydroxyl group. Indeed, it is probable that complexation through the *o*-hydroxyaldehyde moiety occurs in gossypol itself and stabilizes this part of the molecule during attack of the other ring. Jonassen and Demint[6] have postulated for an iron(II)–gossypol complex studied by them that the aldehyde group and the *peri*-hydroxyl (1-hydroxyl) is the site of complexation. Since this *peri*-hydroxyl is obviously involved in our conversion of gossypol to gossypolone and a stable iron complex of gossypolone is isolated from the reaction, it seems likely that Jonassen and Demint had a complex involving the *o*-hydroxyaldehyde moiety. It should be pointed out that the *o*-hydroxyaldehyde complex shows a more stable ring size than the *peri*-hydroxyaldehyde complex (six *vs.* seven) and that in the former complex there are possibilities for delocalization of the negative charge on oxygen not present in the latter case.

Experimental Section[7]

6,6',7,7'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-(2,2'-binaphthalene)-1,1',4,4'-tetraone-8,8'-dicarboxaldehyde ("Gossypolone") (II).—A solution of 2.0 g. (3.5 mmoles) of gossypol acetic acid in 100 ml. of acetone and 200 ml. of acetic acid was heated on a steam bath during the addition of 150 ml. of a 10% aqueous solution of ferric chloride hexahydrate (56 mmoles) and for several minutes longer. The solution was cooled and 250 ml. of water was added to precipitate a dark iron-containing compound which was removed and treated with a mixture of ether and aqueous 20% sulfuric acid. The liberated phenol was taken into the ether layer, this layer was separated and dried, and the ether was evaporated. The residue was recrystallized from aqueous acetic acid to yield 0.9 to 1.3 g. (47–69% yield) of orange product melting at 259° after some prior sintering at about 220°. The melting point could be raised to 264° with additional recrystallization.

Anal. Calcd. for $C_{30}H_{26}O_{10}$: C, 65.93; H, 4.79. Found: C, 65.74, 65.96; H, 4.91, 4.82.

Gossopolone showed a single spot of R_f 0.60 in a thin layer chromatogram on silica gel G with benzene–methanol (95:5) and R_f 0.70 with benzene–dioxane–acetic acid (90:25:4). Gossypolone would not move on the silica gel G coated plates unless the thin layer was given a prior treatment by development of the entire plate with methanol–concentrated hydrochloric acid (9:1). This behavior was apparently caused by iron in the absorbent which complexed the gossypolone.

Gossypolone exhibited the following bands in the visible and ultraviolet regions [in mμ (log ε)]: 223 (4.5), 272 (4.4), 315 (broad shoulder) (4.2), 408 (broad shoulder((3.7). The n.m.r. spectrum of gossypolone is indicated in Table I.

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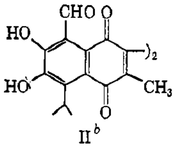
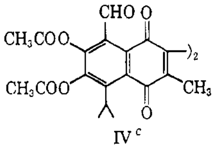
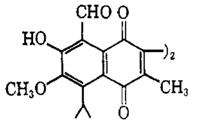
[5] R. Adams and T. A. Geissman, *J. Am. Chem. Soc.*, **60**, 2163 (1938).

[6] H. B. Jonassen and R. J. Demint, *J. Am. Oil Chemists' Soc.*, **32**, 424 (1955).

[7] Infrared spectra are from KBr pellets taken on a Perkin-Elmer Infracord. N.m.r. spectra were determined in $CDCl_3$ and dioxane on a Varian A-60 instrument. Ultraviolet spectra were taken in 95% ethanol on a Cary Model 14 instrument. Thin layer chromatograms were with 300-μ layers of Merck silica gel G and H. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn.

TABLE I

N.M.R. SPECTRA[a]

Compd.	Signal position, p.p.m.	Relative intensity	Multiplicity	Proton assignment
 II^b	1.43	6	Doublet	CH$_3$ of isopropyl
	2.00	3	Singlet	Ring CH$_3$
	8.69	1	Singlet	OH of 6-position
	10.35	1	Singlet	CH of aldehyde
	12.55	1	Singlet	OH of 7-position
 IV^c	1.36	6	Doublet	CH$_3$ of isopropyl
	2.07	3	Singlet	Ring CH$_3$
	2.32	6	Doublet	Acetyl CH$_3$
	4.31	1	Multiplet	CH of isopropyl
	10.00	1	Singlet	CH of aldehyde
 IX^c	1.42	6	Doublet	CH$_3$ of isopropyl
	2.04	3	Singlet	Ring CH$_3$
	4.06 (4.30)	3–4		CH$_3$ of methoxyl + CH of isopropyl
	10.46	1	Singlet	CH of aldehyde
	12.79	1	Singlet	OH of 7-position

[a] Relative to tetramethylsilane as internal standard (TMS = 0). [b] Measured in dioxane, which obscures the 2.2–4.9-p.p.m. region. [c] Measured in CDCl$_3$.

Gossypolone (150 mg.) dissolved in 3 ml. of dioxane and 10 ml. of methanol was treated with a solution of 57 mg. of aniline in 20 ml. of methanol and a dark colored precipitate formed at once. The mixture was heated to boiling briefly, then cooled and filtered to yield 175 mg. (91%) of violet solid. This was recrystallized three times from dioxane–methanol. The melting point of the product was greater than 325°. Thin layer chromatograms on iron-free silica gel G with benzene–dioxane–acetic acid (90: 25:4) showed a single spot of R_f 0.70. Elemental analysis indicated a **dianil derivative of gossypolone** and reaction at the aldehyde carbonyl is postulated as in structure III.

Anal. Calcd. for $C_{42}H_{36}N_2O_8$: C, 72.38; H, 5.21; N, 4.02. Found: C, 72.49; H, 5.24; N, 3.88.

6,6′,7,7′-Tetraacetoxy-5,5′-diisopropyl-3,3′-dimethyl-(2,2′-binaphthalene)-1,1′,4,4′-tetraone-8,8′-dicarboxaldehyde (IV).— A mixture of 500 mg. of gossypolone, 800 mg. of freshly fused sodium acetate, and 5 ml. of acetic anhydride was heated on a steam bath for 15 min. and then poured into ice–water. After several hours the brownish product was filtered off and extracted with 20 ml. of boiling ethanol, and the residue was crystallized from methanol–acetone to give 167 mg. of the tetraacetate. The thin yellow needles melted at 254° with decomposition. The ultraviolet spectrum of the tetraacetate was as follows: 340 mμ (very broad) (log ϵ 3.8), 262 mμ (log ϵ 4.6).

Anal. Calcd. for $C_{38}H_{34}O_{14}$: C, 63.86; H, 4.80. Found: C, 64.15, 64.06; H, 4.81, 4.70.

The tetraacetate IV was also prepared by Clark's[2a] method. The product melted at 244° with decomposition (lit.[2a] m.p. 210–230°). The infrared spectra of the samples prepared by the two different routes were identical as was the behavior on the thin layer chromatographic plates (R_f 0.62, silica gel G, benzene–dioxane–acetic acid, 90:25:4). The n.m.r. spectrum is indicated in Table I.

The **dianil derivative (VI) of the tetraacetate** was prepared in dioxane–methanol from 150 mg. of the tetraacetate and 44 mg. of aniline. The product (52 mg.) was recrystallized from dioxane–water and melted at 284° with decomposition. It gave an R_f value of 0.87 on silica gel H with benzene–dioxane–acetic acid (90:25:4).

Anal. Calcd. for $C_{50}H_{44}N_2O_{12}$: C, 69.43; H, 5.13; N, 3.24. Found: C, 69.57; H, 5.16; N, 3.40.

Oxidation of Gossypol Dimethyl Ether with Ferric Chloride.— This reaction was performed according to Adams.[5] The product melted at 213–215°, lit.[5] m.p. 215–216°. The n.m.r. spectrum, which supports structure IX, is indicated in Table I.

Anal. Calcd. for $C_{32}H_{30}O_{10}$: C, 66.89; H, 5.26. Found: C, 66.78; H, 5.18.

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