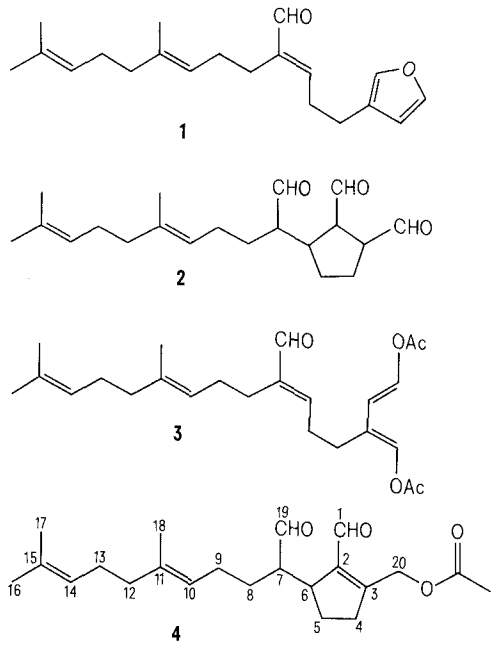
versa. The second possibility was excluded on the basis of additional ^{1}H NMR-data. NOE effect was registered for the 20-H_2 signal while no detectable effect was observed for the 1-H resonance when the 4-H_2 (2.60 ppm) signal was saturated in a difference NOE experiment. Confirming evidence was obtained by mass spectrum which exhibits an intense peak at m/z 342 (10% of the base peak) deriving from the loss of a molecule of water from the 2 aldehydic groups to give a pyrane ring. The mass spectrum shows other significative peaks at m/z 300 (16%, M^+-AcOH), 282 (14%, $300-H_2O$), 231 (8%, $300-C_5H_9$), 107 (91%, $300-C_{13}H_{21}O$) and 69 (base peak, C_5H_9).

UV-spectrum ($\lambda_{max}^{n\text{-hexane}}$ 247 nm, ε 7450) is also consistent with the proposed structure, being indicative of a strained trisubstituted α,β-unsaturated aldehyde.

The carbon skeleton of petiodial has previously been found only in udoteatrial (**2**) and this could have a chemotaxonomic significance.



1 This work is supported by CNR (Roma) in the framework of the 'Progetto Finalizzato Chimica Fine e Secondaria'.
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0014-4754/83/111275-02$1.50+0.20/0

Gossypol. Synthesis and in vitro spermicidal activity of isomeric hemigossypol derivatives[1]

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February 25, 1983

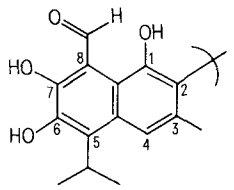
Summary. Three isomeric hemigossypol derivatives (**3**, **4**, **5**) have been synthesized. Two of these derivatives (**3**, **4**) and one synthetic intermediate (**7**) have been shown to have activity comparable to gossypol (**1**) in a sperm motility assay.

Gossypol (**1**), a cotton seed pigment, has been reported[4] to be an effective, reversible orally administered male contraceptive. This antifertility activity has stimulated wide interest in the development of a profile of structure-activity relationships for gossypol (**1**) and its sesquiterpene precursor, hemigossypol (**2**). Although the precise mechanism of action is not clear, it is known that gossypol damages stage 18 and 19 spermatids in the testis[5]. Additionally gossypol has been demonstrated to be an effective spermicidal agent[6]. Because of the instability of hemigossypol and some of its derivatives towards dimerization and the long term nature of in vivo feeding experiments, a rapid, reliable in vitro assay is desirable as an initial screen. For this purpose a sperm motility assay has been developed to measure the in vitro spermicidal activity of the gossypol derivatives with the hope of establishing a correlation between this activity and in vivo antifertility activity similar to that which exists for gossypol itself. We wish to report in this preliminary communication the synthesis of 3 isomeric hemigossypol derivatives (**3**, **4** and **5**) and their effect on sperm motilities.

Chemistry. All 3 of the isomeric naphthaldehydes are the result of regioselective formylations of 1,6,7-trimethoxy-3-methyl-5-(1-methylethyl)naphthalene (**6**). This key inter-

Inhibition of hamster sperm by gossypol derivatives

Compound (50 μM)	% Inhibition (5 min)
1	100
3	84
4	96
5	3
6	4
7	100
9	20



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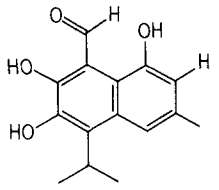

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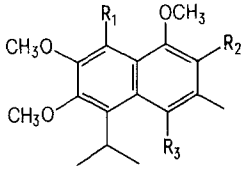
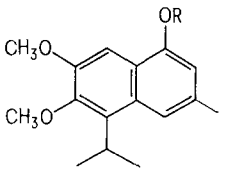
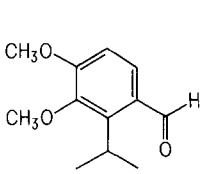


3 R_1 = CHO, R_2 = R_3 = H
4 R_1 = R_3 = H, R_2 = CHO
5 R_1 = R_2 = H, R_3 = CHO



6 R = CH_3
7 R = H



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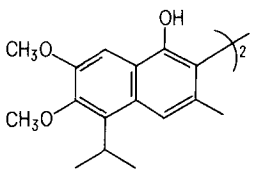

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mediate is available by modification of the procedures of Edwards and Cashaw[7] and the more recent scheme of Venuti[8] from 3,5-dimethoxy-2-(1-methylethyl)benzaldehyde (**8**); in both cases the naphthol (**7**) is produced. This is immediately converted to its trimethyl ether (**6**)[9] because hemigossypol (**2**) and many of its derivatives with a free hydroxyl in the 1-position dimerize rapidly. As an example, we have found that **7** dimerizes rapidly even as a solid, in the cold (−10 °C), under an inert atmosphere, to the apogossypol tetramethyl ether (**9**)[7,8].

By alteration of the formylation procedures, all 3 isomeric aldehydes (**3**, **4** and **5**) are produced from **6**. Metallation of **6** with tert-butyl lithium in pentane/cyclohexane, followed by formylation with N-methylformanilide produced regioselectively the 8-formylnaphthalene (**3**, 64% after chromatography). The structure was based primarily on NMR evidence, broadened aryl proton resonance due to meta coupling[10] as well as intercomparison of the isomers (vide infra). Analogous treatment of **6** with n-butyl lithium in hexane/ether, followed by formylation, resulted in **4**[11] (40% after chromatography), together with a trace amount of **3**. This peri -vs- ortho regioselectivity with tert.-butyl -vs- n-butyl lithium was also observed by Shirley and Cheng[12] during metallation of 1-methoxynaphthalene. Finally the 3rd isomer **5**[13] is also produced from **6** by acidic formylation with $TiCl_4/Cl_2CHOCH_3$ in 70% yield. Here the structure was determined by the sharpness of the aryl proton resonances as well as intercomparison of the isomers. Thus it is possible to introduce a formyl group regioselectively into the naphthalene nucleus of hemigossypol trimethyl ether in order to investigate the positional requirements of the aldehyde group toward spermicidal activity.

Biology. Spermicidal activities were assayed in vitro by incubation of the compounds at concentrations of 50 μM with hamster sperm and measuring the percent motility of the sperm as a function of time. The 50 μM data presented in the table have been normalized to 5 min, the time of complete inhibition of hamster sperm by gossypol (**1**), the standard. The complete description of this assay and its results will be published elsewhere[14]. However, from these early data it can be seen that 3 compounds, **3**, **4** and **7**, have activities comparable to gossypol. Compound **7**, the unstable naphthol that dimerized rapidly, appeared equiactive to gossypol (**1**); its dimer (**9**), however, had little activity. There does not appear to be any obvious structural feature in common among the compounds that show spermicidal activity. Work on gossypol-related compounds is continuing in these laboratories.

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1 Acknowledgment. This work is supported by NICHD NO1-HD-2829.

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10 NMR ($CDCl_3$) δ 1.46 (d, 6H, J7Hz, $CH(CH_3)_2$), 2.48 (S, 3H, $ArCH_3$), 3.80 (M, 1H, $CH(CH_3)_2$), 3.83, 3.85, 3.88 (S, 3H, OCH_3), 6.60 (bS, 1H, ArH), 7.53 (bS, 1H, ArH) and 10.60 (S, 1H, CHO).
11 NMR ($CDCl_3$) δ 1.50 (d, 6H, J7Hz, $CH(CH_3)_2$), 2.71 (S, 3H, $ArCH_3$), 3.93, 4.00, 4.07 (S, 3H, $ArOCH_3$), 4.00 (M, 1H, $CH(CH_3)_2$), 7.42 (S, 1H, ArH), 7.67 (S, 1H, ArH) 10.70 (S, 1H, CHO).
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0014-4754/83/111276-02$1.50 + 0.20/0