

# CHEMISTRY OF GOSSYPOL

## Part V. Products of Acetylation of Gossypol

BY K. SATYANARAYANA MURTY AND T. R. SESHADRI, F.A.Sc.

(From the Departments of Chemistry, Andhra and Delhi Universities)

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THE earlier methods of Carruth<sup>1</sup> and of Clark<sup>2</sup> for the acetylation of gossypol were improved by Adams, *et al.*,<sup>3</sup> who adopted milder conditions. Still they obtained a mixture of two products which was separated by using difference in solubility. One was a colourless substance melting at 279° and was considered to be the normal acetylation product and hence called gossypol hexa-acetate. The second was a yellow substance melting at 186°. It resembled closely the colourless hexa-acetate in all its reactions but it contained more carbon. Its exact nature was not clearly understood and it was called hexa-acetyl gossypol. This was considered to be a later product obtained from the white hexa-acetate by further change. In their more recent paper Boatner, *et al.*<sup>4</sup> consider that the white substance agrees more closely with the requirements of a tetra-acetate and they were not able to obtain evidence that it undergoes change into the yellow acetyl derivative. In a number of our experiments using Adams' method it appeared that the yellow acetyl derivative is more readily formed directly from gossypol than from gossypol hexa-acetate.

In order to be sure of the purity of the products besides other considerations, attempts have now been made to discover methods yielding a single compound. In this we have been successful. The action of acetyl chloride on gossypol in the presence of pyridine and in the cold is free from complications. It gives a good yield of white gossypol acetate as the sole product and it is readily purified.

The complications that were met with in high temperature acetylation of gossypol would appear to be due to the presence of *ortho*-hydroxy aldehyde groups in gossypol capable of undergoing Perkin's reaction. In an earlier paper of this series<sup>5</sup> the presence of two such groups was established by condensation with acetoacetic ester and malonic ester yielding the  $\alpha$ -pyrone derivatives and with acetophenone forming pyrylium salts. By carefully separating the mixture of products obtained by boiling gossypol, sodium acetate and acetic anhydride besides the above mentioned white and yellow

acetyl gossypols a third compound which is more sparingly soluble in solvents and which has a higher melting point could be isolated. This is produced in higher yields on carrying out the heating at 180° for 8 hours. It does not melt below 330° and has the properties of  $\alpha$ -pyrone derivatives discussed in the earlier paper.<sup>5</sup>

#### EXPERIMENTAL

*Acetylation of gossypol using acetic anhydride and pyridine.*—The following procedure is found to be more convenient for getting the white and yellow gossypol acetates.

Gossypol (1 g.) was treated with acetic anhydride (5 c.c.) and pyridine (0.5 c.c.) and the solution gently refluxed for 30 minutes. The reagents were removed under reduced pressure as completely as possible and the highly viscous residue treated with ether (15 c.c.). On allowing to stand for two hours a white crystalline solid separated out which was filtered, washed with a little ether and recrystallised from a mixture of benzene and ligroin. It formed colourless lens-shaped plates melting at 278–79°. Yield, 0.3 g. It was sparingly soluble in ether but readily in chloroform. In concentrated sulphuric acid it dissolved giving a scarlet red colour to the solution.

The ethereal filtrate which contained the second acetate was evaporated completely and treated with water. The pale yellow solid was filtered, washed with water and purified by crystallising twice from ligroin. It was obtained as a pale yellow crystalline solid melting at 180–85° with decomposition. It was readily soluble in the common organic solvents and gave a scarlet red colour with concentrated sulphuric acid.

*Acetylation of gossypol with acetyl chloride.*—Pure gossypol (1 g.) was dissolved in pure anhydrous pyridine (10 c.c.) and the solution cooled in ice. Acetyl chloride (2 c.c.) was then added drop by drop with vigorous stirring during the course of 30 minutes. A white solid separated out during the addition of the reagent. The reaction mixture was allowed to stand for 24 hours and poured into ice-cold water. The solid product was filtered, washed well with water and dried. It was treated with ether and kept for 2 hours whereby the white acetate was obtained almost pure. It was filtered, washed with ether and crystallised from a mixture of benzene and ligroin. It formed colourless lens-shaped plates melting at 278–79°, identical with the white acetate described before. Yield, 0.7–0.9 g. [Found: C, 65.4; H, 5.6;  $C_{30}H_{24}O_2$  (OCOCH<sub>3</sub>)<sub>6</sub> requires C, 65.5 and H, 5.5%.] It is necessary to have quite pure pyridine for the success of the reaction. When this is not assured results are very different.

*Perkin's reaction on gossypol.*—Gossypol (1 g.) was heated with acetic anhydride (10 c.c.) and fused sodium acetate (5 g.) at 180° for 8 hours. The cooled reaction mixture was poured into water and the pale brown solid filtered and washed with water. It was purified by crystallisation from pyridine or ethyl acetate. It was very sparingly soluble in methyl alcohol and other common organic solvents and did not melt below 330°. [Found: C, 68.5; H, 5.3:  $C_{34}H_{26}O_4$  (OCOCH<sub>3</sub>)<sub>4</sub>—(α-pyrone derivative) requires C, 68.7; H, 5.2%.]

When the heating was done only for 2 hours and the crude product boiled with methyl alcohol, a small quantity of a solid not melting below 330° was left undissolved. On allowing the alcoholic solution to stand overnight the white acetate separated and from the mother liquor the yellow acetyl derivative could be obtained.

#### SUMMARY

The white acetate of gossypol is conveniently prepared by employing acetyl chloride and pyridine in the cold for the acetylation. The use of acetic anhydride and a catalyst at elevated temperatures produces a high melting pyrone derivative.

#### REFERENCES

1. Carruth .. *J.A.C.S.*, 1918, 647.
2. Clark .. *J. Biol. Chem.*, 1928, 76, 220.
3. Adams, *et al.* .. *J.A.C.S.*, 1937, 1729.
4. Boatner, *et al.* .. *Ibid.*, 1947, 1268.
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