[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. L. The Isolation of Caoutchicol

BY RUSSELL E. MARKER AND EUGENE L. WITTLE

Led by the possibility of a new and better source of sterols we recently have investigated the non-saponifiable fraction of an acetone extract of crude rubber known as Jelutong.[1]

While the sterol fraction of this substance was found to be quite small, a large quantity of a new substance of triterpenoid character was found to be present and it is the isolation of this substance, which we have named caoutchicol, that is described in this paper.

Preliminary attempts to crystallize the crude "Jelutong" extract showed that it still contained some waxy ester-like substances; so the extract was rehydrolyzed with hot alcoholic potassium hydroxide. The non-saponifiable fraction after this hydrolysis was treated with digitonin to precipitate the sterols, but the quantity of precipitate which was thus formed was too small to permit a characterization of the sterols which it contained. The main constituent, which did not precipitate digitonin, was found to be an alcohol, caoutchicol, which was purified most easily by the preparation and crystallization of its high melting acetate. Hydrolysis of this acetate gave the original caoutchicol, for which analysis and molecular weight indicate the formula $C_{30}H_{50}O$. This compound possesses one active double bond as shown by the formation of a crystalline dibromide from both caoutchicol and its acetate, and also the formation of a dihydro derivative by catalytic reduction in acetic acid using Adams catalyst. This dihydro compound is saturated to bromine. A further proof that the substance contains only one hydroxyl group is the preparation of a ketone, dihydrocaoutchicone, by oxidation of the dihydro compound with chromic acid. This ketone was characterized by the formation of a semicarbazone. The fact that caoutchicol possesses thirty carbon atoms and does not precipitate digitonin suggests that it is closely related to the triterpenoids, and is probably not a sterol. Thus, it may be related to lanosterol and agnosterol.

We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous help and assistance in various phases of this work.

Experimental Part

Caoutchicol.—The non-saponifiable fraction of an acetone extract of crude rubber known as Jelutong was supplied to us by the B. F. Goodrich Company of Akron, Ohio. This product (35 g.) was resaponified by refluxing for one hour with alcoholic potassium hydroxide solution. Water was added and the product was filtered. It was dried by distilling benzene from it. The product was dissolved in 250 cc. of ethyl alcohol, and to this was added 5 g. of digitonin dissolved in 250 cc. of hot ethyl alcohol. After standing overnight the digitonide was filtered and dried (wt. 5.4 g.). After decomposition with pyridine it gave a mixture of sterols which could not be separated because of the small quantity available.

The alcohol was removed from the filtrate of the digitonide and the residue was extracted with ether and filtered from unchanged digitonin. It was dried by distilling benzene from it, then converted into its acetate by refluxing with 100 cc. of acetic anhydride for thirty minutes. The product was collected at 0° and recrystallized from acetone and methanol. It is very insoluble in methanol and fairly soluble in acetone, crystallizing in needles melting at 216°.

Anal. Calcd. for $C_{32}H_{52}O_2$: C, 81.9; H, 11.2; mol. wt., 468. Found: C, 81.8; H, 11.2; mol. wt. (Rast), 472.

To a solution of 100 mg. of the acetate of caoutchicol in 5 cc. of ether was added a slight excess of molar bromine solution in acetic acid. The ether was evaporated and the residue was crystallized from acetone. It melted at 225° with decomposition.

Anal. Calcd. for $C_{32}H_{52}O_2Br_2$: C, 61.1; H, 8.4. Found: C, 61.1; H, 8.3.

A solution of 100 mg. of the acetate of caoutchicol in alcohol was hydrolyzed by refluxing with alcoholic potassium hydroxide for thirty minutes. After crystallization from methanol and acetone, it melted with decomposition at 205–210°, and gave no precipitate with alcoholic digitonin.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.4; H, 11.8. Found: C, 84.6; H, 11.8.

To a solution of 100 mg. of caoutchicol dissolved in 5 cc. of ether was added a slight excess of a molar bromine solution in acetic acid. The ether was evaporated and the residue was crystallized from acetone. It melted at 186–190° with decomposition.

Anal. Calcd. for $C_{30}H_{50}OBr_2$: C, 61.4; H, 8.6. Found: C, 60.9; H, 8.4.

Dihydrocaoutchicol Acetate.—A solution of 1 g. of caoutchicol acetate in 100 cc. of acetic acid was shaken with 500 mg. of platinum oxide under a pressure of 45 pounds (3 atm.) of hydrogen at 70° for three hours. The catalyst was filtered, the solvent removed, and the residue crystallized from acetone, methanol, and acetic acid. It melted at 247°.

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[1] Kindly supplied by B. F. Goodrich Company, Akron, Ohio.

Anal. Calcd. for $C_{32}H_{54}O_2$: C, 81.6; H, 11.6. Found: C, 81.6; H, 11.4.

Dihydrocaoutchicol.—A solution of 500 mg. of dihydrocaoutchicol acetate in alcohol was refluxed with an excess of alcoholic potassium hydroxide for thirty minutes. After crystallization from acetone and methanol, the product had a melting point of 188°.

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.0; H, 12.2. Found: C, 83.8; H, 12.1.

Dihydrocaoutchicone.—To a solution of 200 mg. of dihydrocaoutchicol in 20 cc. of acetic acid was added 60 mg. of chromic oxide in 3 cc. of 90% acetic acid. After standing at room temperature for one hour the crystalline product which separated was filtered and recrystallized from acetone to a constant melting point of 210°.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.4; H, 11.8. Found: C, 84.2; H, 11.8.

A solution of 20 mg. of dihydrocaoutchicone in alcohol was heated on a steam-bath with 20 mg. of semicarbazide hydrochloride and 20 mg. of sodium acetate for one hour. It was poured into water, filtered and recrystallized from acetone to give the semicarbazone, m. p. 249–250°, dec.

Anal. Calcd. for $C_{31}H_{53}N_3O$: C, 77.0; H, 11.0. Found: C, 76.9; H, 11.0.

Summary

Caoutchicol ($C_{30}H_{50}O$), a new alcohol, was isolated from a crude rubber extract (Jelutong). It does not precipitate digitonin. It forms a monoacetate, a dibromide and can be reduced to a dihydro derivative. Dihydrocaoutchicol forms the ketone, dihydrocaoutchicone, on oxidation.

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Sterols. LI. Δ^4-Pregnenone-3

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As a by-product of the preparation of progesterone by the debromination of progesterone dibromide with zinc, Butenandt and Westphal[1] obtained $\Delta^{4,5}$-pregnenone-20. This compound was found to have no progestational activity. In order to determine the particular structural features essential for progestational activity, and for purposes of comparison with new compounds isolated from urines, we have now prepared Δ^4-pregnenone-3.

The starting material for this preparation, pregnanol-3(α), has been described in a previous publication.[2] In that work it was shown that the Clemmensen reduction of pregnanol-3(α)-one-20 gave 50% yields of pregnanol-3(α). Since then we have found that the Wolff–Kishner reduction of pregnanol-3(α)-one-20 gives considerably higher yields (85%) although the product is contaminated with some of the epimer, pregnanol-3(β). The pregnanol-3 mixture so obtained was oxidized to pregnanone-3 and the latter brominated in acetic acid. The 4-bromopregnanone-3 formed was refluxed with pyridine, and worked up in the usual fashion. The Δ^4-pregnenone-3 proved to be rather difficult to purify because of its low melting point and great solubility in ordinary solvents. By filtering it through a column of activated alumina, and letting it stand for several weeks in dilute alcohol solution it was finally obtained as long needles, m. p. 90°. In harmony with its structure as an α,β-unsaturated diketone, it formed a deep red 2,4-dinitrophenylhydrazone.[3]

As a by-product in the preparation of Δ^4-pregnenone-3 from 4-bromopregnanone-3, the corresponding pyridinium bromide was obtained. Its structure is proved by the analytical data, the fact that it contains an ionizable bromine atom, and the fact that it gives a yellow color with alkali. The latter reaction is characteristic of pyridinium bromides derived from α-bromo ketones.[4]

We wish to thank Dr. Oliver Kamm and Parke, Davis and Company for their generous help and assistance in the various phases of this work.

Experimental

Pregnanol-3(α).—A mixture of 1 g. of pregnanol-3(α)-one-20 (from human pregnancy urine), 0.6 g. of semicarbazide hydrochloride, 0.9 g. of sodium acetate, and 20 cc. of alcohol was refluxed for three hours. The mixture was diluted with 200 cc. of water and the precipitated semicarbazone collected and washed with alcohol and ether; yield, 1.12 g.; m. p. 246°.

To a solution of 1 g. of sodium in 12 cc. of absolute alcohol 1.12 g. of pregnanol-3(α)-one-20 semicarbazone was added, and the mixture heated in a bomb tube for seven hours at 180°. The contents were washed out of

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[1] Butenandt and Westphal, *Ber.*, **67**, 2085 (1934).

[2] Marker and Lawson, THIS JOURNAL, **60**, 2438 (1938).

[3] Mason, Hoehn, McKenzie and Kendall, *J. Biol. Chem.*, **120**, 734 (1937).

[4] Kröhnke, *Ber.*, **66**, 604 (1933).