[CONTRIBUTION FROM THE PEARSON MEMORIAL LABORATORY OF TUFTS COLLEGE]

Chloropropyl Yohimbate and its Derivatives

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It has been shown[1] that yohimbic acid condenses with ethylene chlorohydrin to form a halogenated ester that reacts smoothly with secondary amines. Since the resulting derivatives are physiologically active, in the form of the water-soluble hydrochloric acid salts, similar compounds have been synthesized from trimethylene chlorohydrin. Also the cetyl and benzyl esters of yohimbic acid were prepared. Cetyl yohimbate is the ester of the hydrated form of yohimbic acid, but it does not lose the additional molecule of water on drying. The hydrochloric acid salt is insoluble in water. Otherwise the properties of the new substances are similar to those previously prepared.

Experimental

α-Chloropropyl Yohimbate.—A mixture containing 10 g. of yohimbic acid and 50 cc. of trimethylene chlorohydrin saturated with hydrogen chloride gas for a week was added slowly to dilute ammonia solution. The product was crystallized from dilute alcohol, separating in prismatic plates melting at 110–111°; yield nearly 10 g.

Anal. Calcd. for $C_{23}H_{31}O_4N_2Cl$: Cl, 8.2. Found: Cl, 8.2.

A weighed sample lost the equivalent of one mole of water on drying in a vacuum, a loss that was regained by a few minutes of exposure to the air. It reacted in the normal manner with methyl iodide and with hydrochloric acid.

α-Chloropropyl Yohimbate Sulfuric Acid Ester.—Prepared by pouring on cracked ice a solution of the above ester in ten volumes of cold concd. sulfuric acid. The amorphous precipitate was thoroughly washed with water and air dried. It decomposed at 283°.

Anal. Calcd. for $C_{23}H_{31}O_7N_2SCl$: S, 6.2. Found: S, 6.1.

α-Chloropropyl Apoyohimbate.—The sulfuric acid derivative (4 g.) was heated to 70° for a few minutes with 2% potash. The insoluble product was crystallized from dilute alcohol, separating in lustrous plates melting at 105–106° with some decomposition; yield approximately one gram.

Anal. Calcd. for $C_{23}H_{29}O_3N_2Cl$: Cl, 8.5. Found: Cl, 8.4.

The anhydro form was obtained by drying in a vacuum over sulfuric acid. The methyl iodide derivative and hydrochloric acid salt were prepared and analyzed.

α-Diethylaminopropyl Yohimbate.—A sealed tube containing 5 g. of the chloropropyl ester together with an equal weight of diethylamine was heated to 100° for three hours. The mixture worked up in the customary manner yielded 5.5 g. of an amorphous solid that softened above 75° and melted indefinitely.

Anal. Calcd. for $C_{27}H_{41}O_4N_3$. N, 8.9. Found: N, 8.8.

The hydrochloric acid salt and methyl iodide addition product were obtained as crystalline solids melting, respectively, at 192–193° and 195–196°.

Anal. Calcd. for $C_{27}H_{41}O_4N_3 \cdot 2HCl$: Cl, 13.0. Found: Cl, 12.8.

The apo form of the diethylamino derivative was obtained through the sulfuric acid ester as irregular plates (from dilute alcohol) melting at 95–96°.

Anal. Calcd. for $C_{27}H_{39}O_3N_3$: N, 9.3. Found: N, 9.3.

α-Piperidinopropyl Yohimbate.—Formed by heating under a reflux condenser for several minutes the chloro compound with 5 volumes of piperidine. It was obtained as a crystalline powder, from dilute alcohol, melting at 107–108°.

Anal. Calcd. for $C_{28}H_{41}O_4N_3$: N, 8.7. Found: N, 8.7.

Cetyl Yohimbate.—A mixture of 10 g. of yohimbic acid with 3–4 volumes of cetyl alcohol was heated until the alcohol melted. It was then saturated with hydrogen chloride gas and kept at 50–55° for a day, after which it was extracted with hot acetone. The residue following trituration with dilute ammonia was dissolved in alcohol and added slowly to cold water. The ester was obtained as a tacky gum, although at 0° it changed into a wax-like solid. It did not change weight on drying over sulfuric acid in a vacuum.

Anal. Calcd. for $C_{36}H_{58}O_4N_2$: N, 4.8. Found: N, 4.6.

The hydrochloric acid salt, small crystals melting at 238°, is insoluble in water.

Anal. Calcd. for $C_{36}H_{58}O_4N_2 \cdot HCl$: Cl, 5.7. Found: Cl, 5.7.

Benzyl Yohimbate.—Prepared by a procedure similar to that used with cetyl alcohol as an amorphous powder partially melting at 77–78°. It changed into the anhydro form when dried in a vacuum over sulfuric acid.

Anal. Calcd. for $C_{27}H_{32}O_4N_2$: N, 6.3. Found: N, 6.4.

The hydrochloric acid salt obtained as a crystalline powder from alcohol–acetone mixture and melting at 253–254° is only moderately soluble in water.

Anal. Calcd. for $C_{27}H_{32}O_4N_2 \cdot HCl$: Cl, 7.3. Found: Cl, 7.2.

Summary

Esters of yohimbic acid with cetyl alcohol, benzyl alcohol and trimethylene chlorohydrin have been synthesized and certain derivatives prepared.

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(1) Worrall, THIS JOURNAL, **55**, 3715 (1933).