which are characteristic of hexaarylethanes and must therefore be classed as a new type of hydrocarbon which contains an active carbon–carbon single bond.

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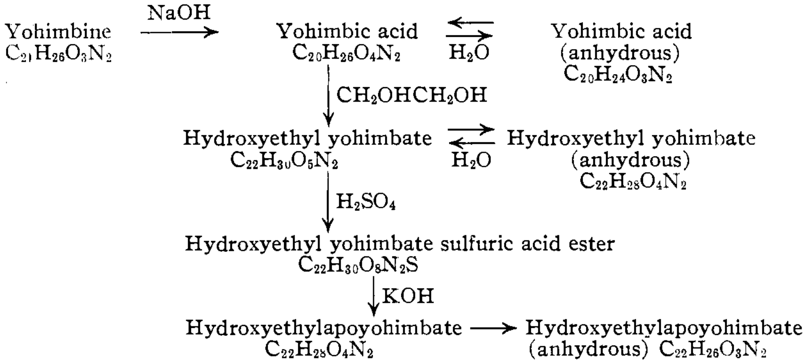
Some Hydroxy and Amino Esters of Yohimbic Acid

BY DAVID E. WORRALL

Yohimbine is an optically active alkaloid occurring in the bark of the African yohimbus tree. The present investigation is concerned with an attempt to increase the anesthetic action by the introduction of certain groups. Yohimbic acid exists in two forms differing one from the other by a molecule of water. Yohimbine is the methyl ester of anhydrous yohimbic acid and results whether one starts with hydrated or anhydrous yohimbic acid. Similarly ethyl alcohol forms an ester with yohimbic acid corresponding to the anhydrous form. On the contrary, propyl and butyl alcohols form esters that retain the additional molecule of water.[1]

It has been found in the present investigation that yohimbic acid forms esters with the polyhydric alcohols, ethylene glycol, trimethyleneglycol and glycerol, as well as with ethylene chlorohydrin, reacting with one equivalent of each. The resulting esters are derivatives of the hydrated form of yohimbic acid. The additional molecule of water is easily eliminated by drying in a vacuum over phosphorus pentoxide, a process that is reversed by exposing the product to air. The new esters turn yellow on exposure to light, form water-soluble salts with acids, etc. Esters are formed with sulfuric acid that on hydrolysis with alkali regenerate sulfuric acid, thereby producing an unsaturated group in the alkaloid. This reaction results in a base containing one molecule less of water than the



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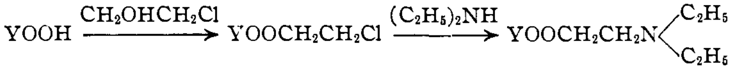
[1] Barger and Field, *J. Chem. Soc.*, **123**, 3003 (1923).

original substance. The new substance is still capable of losing a molecule of water, changing from the hydrated to anhydrous form. Therefore, the term *apo* introduced by Barger and Field,[2] who discovered this reaction with sulfuric acid, has been used to designate the unsaturated base. The scheme shown, using ethylene glycol with yohimbic acid, illustrates the changes and relationships involved.

The ester obtained from ethylene chlorohydrin is capable of condensing with secondary amines, thereby producing groups found in local anesthetics of the novacaine type.



$$\mathrm{YOOH} \xrightarrow{\mathrm{CH_2OHCH_2Cl}} \mathrm{YOOCH_2CH_2Cl} \xrightarrow{\mathrm{(C_2H_5)_2NH}} \mathrm{YOOCH_2CH_2N}\begin{cases}\mathrm{C_2H_5}\\ \mathrm{C_2H_5}\end{cases}$$

Experimental

Yohimbic acid was prepared by the alkaline hydrolysis of yohimbine hydrochloride:[3] 5-g. samples were weighed out, mixed with 20–25 cc. of the appropriate alcohol and saturated with hydrogen chloride gas. The crude ester solutions after a week's standing were added slowly to a moderately large volume of water containing an excess of ammonia and recrystallized from dilute alcohol; yield of purified material 3–3.5 g.

TABLE I

ESTERS OF YOHIMBIC ACID

Substance	Formula	M. p., °C.	Cryst. form	Analyses, % Calcd. C	Calcd. H	Found C	Found H
α-Chloroethyl	$C_{22}H_{29}O_4N_2Cl$	119–120	Stout flat needles	Cl,	8.4	Cl,	8.4
α-Hydroxyethyl	$C_{22}H_{30}O_5N_2$	132–135	Prismatic needles	65.7	7.5	65.2	7.6
α-Hydroxypropyl	$C_{23}H_{32}O_5N_2$	135–138	Flat needles	66.4	7.7	66.0	7.8
α,β-Dihydroxypropyl	$C_{23}H_{32}O_6N_2$	111–112	Microscopic	63.9	7.4	63.5	7.5

The new esters, if dried in a vacuum over sulfuric acid, gain weight on exposure to the atmosphere until one molar equivalent of water has been absorbed.

α-Hydroxyethyl Yohimbate Sulfuric Acid Ester.—One gram of hydroxyethyl yohimbate was dissolved in 10 cc. of cold concd. sulfuric acid, warmed to room temperature and poured on cracked ice. The product was recrystallized from water, separating in the form of microscopic crystals melting at 288–289°.

Anal. Calcd. for $C_{22}H_{30}O_8N_2S$: S, 6.6. Found: S, 6.7.

α-Hydroxyethyl Apoyohimbate.—The sulfuric acid ester was heated for a few minutes with dilute alkali. Extraction with ether removed the apo compound, which was recrystallized from alcohol, separating in glistening irregular plates melting at 117–118°, and darkening rapidly on exposure to light or heat.

Anal. Calcd. for $C_{22}H_{28}O_4N_2$: C, 68.7, H, 7.3. Found: C, 68.2, H, 7.4.

The hydrochloric acid salt, prepared by adding a few drops of the acid to a hot alcoholic solution of the ester, separates from solution in clusters of flat needles melting with decomposition at 292–294°.

Anal. Calcd. for $C_{22}H_{28}O_4N_2{\cdot}HCl$: Cl, 8.4. Found: Cl, 8.2.

The amine derivatives were prepared by dissolving chloroethyl yohimbate in an excess of the appropriate amine and heating the mixture in a sealed tube. The contents were then dissolved in acid and precipitated in the customary manner with ammonia. The anhydrous form in each case was used for analysis.

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[2] Barger and Field, *J. Chem. Soc.*, **123**, 1040 (1923).

[3] Spiegel, *Ber.*, **36**, 169 (1903); Field, *J. Chem. Soc.*, **123**, 3004 (1923).

TABLE II

AMINO ESTERS OF YOHIMBIC ACID

Substance	Formula	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Time required for formation
α-Diethylaminoethyl	$C_{26}H_{37}O_3N_3$	76– 78	71.1	8.4	70.8	8.9	3 hours
α-Allylaminoethyl	$C_{25}H_{33}O_3N_3$	124–126	70.9	7.8	70.4	7.9	8 hours
α-Piperidinoethyl	$C_{27}H_{39}O_4N_3$	129–131	69.1	8.3	69.4	8.6	10 minutes

α-Diethylaminoethyl Apoyohimbate.—The diethylamino compound (5 g.) was dissolved in 50 cc. of cold concd. sulfuric acid. After standing for ten minutes the mixture was added to cracked ice, thereby producing a sticky gelatinous precipitate. This product was converted into the apo compound by heating with 2% alcoholic potash; yield approximately 1 g. The analytical sample was dried over sulfuric acid immediately before use. It separates from alcohol in lustrous microscopic crystals melting at 80–82°.

Anal. Calcd. for $C_{26}H_{35}O_2N_3$: C, 74.1; H, 8.3. Found: C, 73.6; H, 8.5.

These yohimbine compounds react smoothly with methyl iodide, forming addition products which were obtained as follows. To approximately 0.5 g. of the yohimbine derivative dissolved in 5 cc. of acetone was added an excess of methyl iodide. The resulting oil was separated, washed with acetone and dried at 105–110°.

TABLE III

METHYL IODIDES OF YOHIMBATES

Substance, yohimbate	Formula	Iodine, % Calcd.	Iodine, % Found	M. p., °C.
α-Hydroxypropyl	$C_{23}H_{32}O_5N_2{\cdot}CH_3I$	22.6	22.7	Indefinite
α,β-Dihydroxypropyl	$C_{23}H_{32}O_6N_2{\cdot}CH_3I$	22.1	22.2	Indefinite
α-Allylaminoethyl	$C_{25}H_{35}O_4N_3{\cdot}CH_3I$	21.8	21.6	Indefinite
α-Piperidinoethyl	$C_{27}H_{39}O_4N_3{\cdot}2CH_3I$	33.1	32.9	218–219
α-Diethylaminoethyl	$C_{26}H_{39}O_4N_3{\cdot}2CH_3I$	34.3	34.6	217–218
α-Diethylaminoethyl apo-	$C_{26}H_{37}O_3N_3{\cdot}2CH_3I$	35.1	35.3	179–180

The hydrochloric acid salts were prepared by bubbling hydrogen chloride gas through an acetone solution of the yohimbate and drying in the oven at 105°.

TABLE IV

HYDROCHLORIDES OF YOHIMBATES

Substance, yohimbate	Formula	Chlorine, % Calcd.	Chlorine, % Found	M. p., °C.
α-Allylaminoethyl	$C_{25}H_{35}O_4N_5{\cdot}2HCl$	13.8	14.0	263–264° + foaming
α-Piperidinoethyl	$C_{27}H_{39}O_4N_3{\cdot}2HCl$	13.1	13.0	212–214° + dec.
α-Diethylaminoethyl	$C_{26}H_{39}O_4N_3{\cdot}2HCl$	13.4	13.2	198–200° + foaming

Anal. Calcd. for $C_{26}H_{39}O_4N_3{\cdot}2HCl$: C, 58.9; H, 7.7. Found: C, 58.6; H, 7.8.

Several of these substances have been sent for physiological investigation to Dr. Albert G. Young of Boston for whose assistance in securing the gift of a generous quantity of this alkaloid from Hoffmann-Laroche of Nutley, New Jersey, I am very grateful.

Summary

Esters of yohimbic acid with ethylene glycol, trimethylene glycol, glycerol and ethylene chlorohydrin have been synthesized.

The ester with ethylene chlorohydrin has been found to react with allylamine, piperidine and diethylamine.

Certain salts and derivatives of the resulting hydroxy and amino esters were prepared.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

Studies in the Rearrangements of Phenyl Ethers. The Action of Aluminum Chloride on Butyl Phenyl Ethers

BY RICHARD A. SMITH

The action of aluminum chloride on phenyl ethers has been studied extensively; this reaction is now reasonably clear and is known as the Fries migration.[1]

The isomerization of phenyl ethers to substituted phenols has received but little study; the two rearrangements appear, at the present time, to have many characteristics in common. There are undoubtedly many recorded instances of reactions in which phenyl ether isomerization took place due to the presence of an aluminum chloride catalyst. The transitory nature of the ether in most cases prevented the observation of the rearrangement as such. In 1892 Hartmann and Gattermann[2] in utilizing the action of aluminum chloride at elevated temperatures to hydrolyze phenyl ethers to phenols and alkyl halides noticed, in one case, the formation of a small quantity of a substituted phenol. This will be referred to in greater detail later. Ether rearrangements with the aid of aluminum chloride have been reported by Huston.[3] The author has reported the synthesis of thymol and an isomer by the catalytic isomerization of isopropyl *m*-cresyl ether with aluminum chloride.[4]

In this communication it is desired to show extensions of the method to rearrangements of different types of alkyl phenyl ethers. Ethers in which the carbon atom of the alkyl group attached to the ether oxygen was, respectively, primary, secondary and tertiary were studied. The three butyl ethers, iso, secondary and tertiary, were selected. A second purpose is to attempt to clarify contradictory evidence in the literature pertaining to para iso and tertiary butyl phenols.

The first purpose of the report was fulfilled by synthesizing the three designated butyl phenyl ethers in a conventional manner. The isobutyl phenyl ether has been prepared previously.[2,5]

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(1) Kraenzlein, "Aluminiumchlorid in der organischen Chemie," Verlag Chemie, G. m. b. H., Berlin, 1932.

(2) Hartmann and Gattermann, *Ber.*, **25**, 3531 (1892).

(3) R. C. Huston, Indianapolis Meeting of the American Chemical Society, 1931.

(4) Smith, THIS JOURNAL, **55**, 849 (1933).

(5) Riess, *Ber.*, **3**, 780 (1870); Bamberger, *ibid.*, **19**, 1820 (1885); Perkin, *J. Chem. Soc.*, **69**, 1250 (1896); Senkowski, *Ber.*, **24**, 2974 (1891).