The infrared spectrum of the amino acid salt (in Nujol) showed a strong band at 3190 (OH and NH bands), three weak bands at 2520, 2600, and 2750 (ammonium ion) and a sharp strong band at 1715 cm.$^{-1}$ (C=O of CO_2H group).

An aqueous solution of the benzenesulfonic acid salt (0.52 g. in 100 ml. water) was passed through a column of ion exchange resin (IRA 400 in the acetate form). Evaporation of the eluate afforded the amino acid (0.2 g.), m.p. 265°. Recrystallization from ethanol ether raised the m.p. to 266°.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.90; H, 8.44; N, 9.03. Found: C, 61.98; H, 8.43; N, 8.99.

The *benzenesulfonyl derivative* of the amino acid was prepared by the Schotten-Baumann method and after crystallization from ethanol melted at 173–174°.

Anal. Calcd. for $C_{14}H_{17}NO_4S$: C, 56.94; H, 5.81; N, 4.74. Found: C, 56.74; H, 5.75; N, 5.18.

The infrared spectrum (in Nujol) had a sharp band at 3320 (NH, OH absorption) and at 1682 cm.$^{-1}$ (C=O of CO_2H).

This derivative was also formed when *endo*-2-benzenesulfonamido-3-carboxy-5-norbornene (VII) was hydrogenated over platinum in ethanol. The derivative of the reduced product melted at 173–174°, did not show any melting point depression, and had an identical infrared spectrum as the compound prepared from III above.

Acknowledgment. The authors thank the Research Corp. for a Frederick Gardner Cottrell grant which made this work possible. We would also like to express our appreciation to Mr. Ronald Wilbois for technical help, to Messrs. James Brader and Paul McMahon for determining the infrared spectra. The National Aniline Division of the Allied Chemical and Dye Corp. is also thanked for their generous supply of the anhydrides used.

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[Contribution from the Department of Chemistry of the University of Michigan]

Reactions of the Mono-*p*-toluenesulfonic Acid Ester of Yohimbyl Alcohol[1,2]

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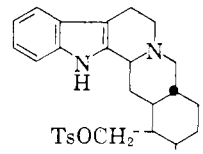
Received March 24, 1959

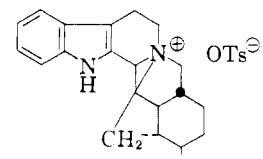
Yohimbyl alcohol mono-*p*-toluenesulfonate alkylates representative alcohols and amines with the formation of ethers of yohimbyl alcohol and 16-aminomethyl derivatives of yohimbol, respectively. Acid hydrolysis of yohimbyl alcohol mono-*p*-toluenesulfonate regenerates yohimbyl alcohol. On the other hand, attempted basic hydrolysis of the ester resulted in intramolecular alkylation of the C-17 hydroxyl group with the formation of an oxetane.

The mono-*p*-toluenesulfonic acid ester (tosyl ester) of yohimbyl alcohol (I) was first prepared by one of us[3] by unimolecular tosylation of yohimbyl alcohol for use as a model compound in connection with projected degradation studies on the alkaloid alstonine. Subsequent investigations required the preparation of fairly large amounts of the ester during the purification of which an interesting, if not entirely unpredictable behavior, was noted. In the present communication, we wish to present certain observations on the behavior of I under a variety of conditions.

At the outset it was noted that, whereas small amounts of I could be recrystallized without difficulty from ethanol, when similar recrystallization of larger amounts of the ester (m.p. 147°) was attempted, a high melting substance (279°) resulted. The infrared spectrum of this high melting compound showed absorption bands at 8.56, 8.95, 9.71, and 9.94μ characteristic of those ascribed to the *p*-toluenesulfonate anion and reminiscent of the absorption displayed by the product of the action of tosyl chloride on reserpinol in pyridine.[4,5]



I



II

Subsequent investigation showed that a substance of similar high melting point was more readily obtained by refluxing I in the higher boiling isoamyl alcohol. After recrystallization from ethanol, material thus prepared furnished analytical data in approximate agreement with those demanded by an internal alkylation product of the type of II solvated by one molecule of ethanol. Subsequent experiments were done with material prepared in this manner. In order to avoid solvation, subsequent batches were recrystallized from acetone.

However, there are obvious difficulties in such a simple interpretation of the formation of the high

(1) This work was supported in part by a Research Grant (H-1733) from the National Heart Institute and in part by a Research Grant (CY-2961) from the National Cancer Institute.

(2) Portions of the work here presented are taken from a dissertation submitted by Kenneth K. Wyckoff in partial fulfillment of requirements for the degree of Doctor of Philosophy in the University of Michigan.

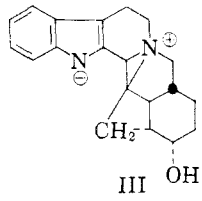
(3) R. C. Elderfield and A. P. Gray, *J. Org. Chem.*, **16**, 506 (1951).

(4) P. A. Diassi, F. L. Weisenborn, C. M. Dylion, and O. Wintersteiner, *J. Am. Chem. Soc.*, **77**, 4687 (1955).

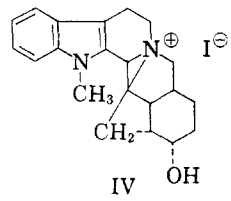
(5) E. E. van Tamelen and P. D. Hance, *J. Am. Chem. Soc.*, **77**, 4692 (1955).

melting compound. The accepted conformation of reserpine with Rings D and E in a *cis* arrangement[6] easily permits formation of such an internal bridge. However, the *trans* D/E ring juncture of yohimbine[7-9] effectively prohibits formation of a compound of the type of II.

The high melting tosylate on successive treatment with sodium hydroxide and methyl iodide furnished a methiodide. If transannular alkylation had occurred the structure of the free base would be represented by the zwitter ion (III) and the methiodide would carry the methyl group on the indole nitrogen (IV).[10]



III

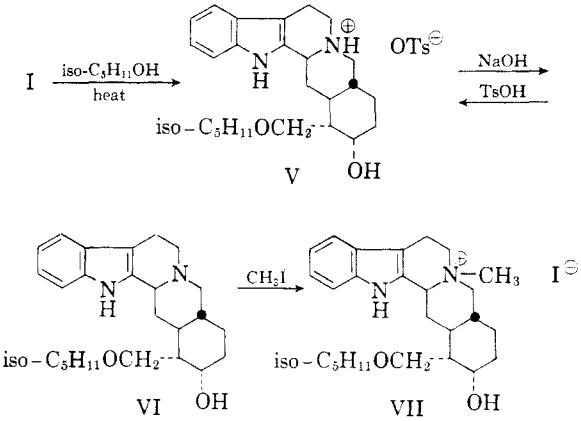


IV

Again, the analytical data for the methiodide were suggestive, although not in perfect agreement with those demanded by IV.

The first positive indication that transannular alkylation had indeed not occurred was the appearance of a strong N—H absorption band at 2.92μ in the infrared spectrum of the above methiodide. It has long been known that *p*-toluenesulfonic acid esters can function as alkylating agents. As a possible explanation for the formation of the ionic tosylate when yohimbyl alcohol monotosyl ester is refluxed with isoamyl alcohol, the possibility of alkylation of the alcohol by the ester immediately comes to mind. In this event, the structure of the ionic tosylate would be represented by the *p*-toluenesulfonic acid salt of the isoamyl ether of yohimbyl alcohol (V).

The free base obtained on treatment of V with sodium hydroxide melted at 101–102°. Careful drying of this material appeared to lead to the loss of about half a molecule of water and gave a substance, m.p. 160–161°. Recrystallization of this from aqueous acetone gave the low melting (101–102°) hydrate. Further, reaction of the compound, m.p. 160–161° with *p*-toluenesulfonic acid resulted in the formation of the original *p*-toluenesulfonic acid salt, m.p. 279°. Reconsideration of the analytical data obtained for this series of compounds resolved the irritating minor divergencies previously discussed and the data now agreed well with those demanded on the assumption of ether formation (VI for the free base and VII for its methiodide).



This interpretation was supported by the results of potentiometric titrations of V and representative model compounds in 50% methanol. According to Diassi and co-workers[6] methyl reserpate (4–18) quaternary tosylate cannot be titrated as a base with perchloric acid in acetic acid, nor as an acid with sodium hydroxide in 67% dimethylformamide. This is to be expected for the behavior of a salt of a strong acid with a strong base. However, when V was titrated with sodium hydroxide, a definite titration curve was obtained from which a molecular weight of 568.3 was calculated. This compares with 568.7 demanded by V. *N*-Ethylpiperidine metho-*p*-toluenesulfonate and yohimbyl alcohol metho-*p*-toluenesulfonate were similarly titrated. Both substances gave titration curves similar to those for weak acids. However, the calculated molecular weights showed large deviations from the theoretical values: + 234% for the yohimbyl alcohol salt and + 585% for the piperidine salt, indicating that these representative quaternary salts cannot be titrated as acids. In contrast, titration of the *p*-toluenesulfonic acid salts of yohimbyl alcohol and of *N*-ethylpiperidine gave molecular weight values within 3% of those calculated. These data support the formulation of V as indicated.

If V correctly represents the structure of the so-called ionic tosylate, other ethers of yohimbyl alcohol should result when I is heated with appropriate alcohols. This has been found to be true. Ethers of yohimbyl alcohol with 2-hexanol, 2-butanol, ethanol, 1-octanol, 2-propanol, and 4-heptanol have been prepared. Pertinent data are given in Tables I and II.

We have also investigated the alkylation of representative amines by I. This reaction was complicated by the formation of intractable tars in many instances. From the reaction of I with 16 amines, well defined alkylated products were obtained from five. With sterically hindered or low-boiling amines, no alkylation could be detected.

(6) P. A. Diassi, F. L. Weisenborn, C. M. Dylion, and O. Wintersteiner, *J. Am. Chem. Soc.*, **77**, 2028 (1955).

(7) G. Stork and R. K. Hill, *J. Am. Chem. Soc.*, **76**, 949 (1954); **79**, 495 (1957).

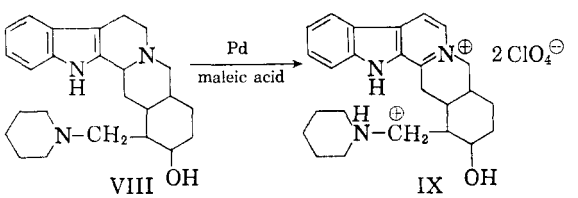
(8) E. E. van Tamelen and M. Shamma, *J. Am. Chem. Soc.*, **76**, 951 (1954). See also *J. Am. Chem. Soc.*, **80**, 5006 (1958).

(9) B. Witkop, *J. Am. Chem. Soc.*, **71**, 2559 (1949).

(10) *cf.* R. B. Woodward and B. Witkop, *J. Am. Chem. Soc.*, **71**, 379 (1949); H. Schwarz, *Experientia*, **6**, 331 (1950) *inter alia*.

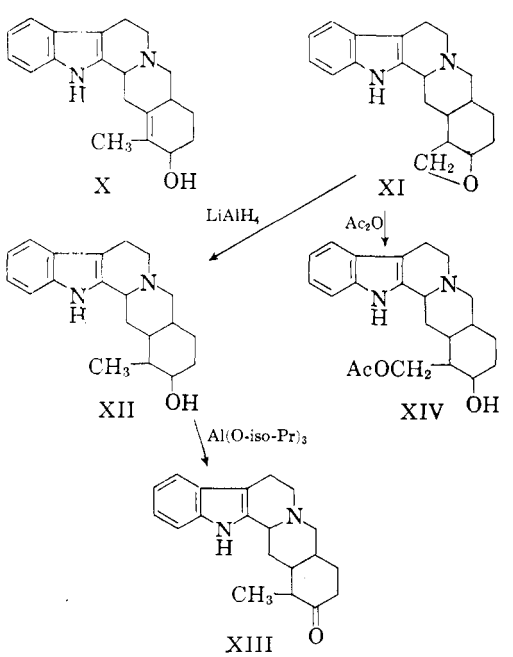
Pertinent data are given in Table III. Amines which gave either intractable tars, or recovered starting material, were aniline, *p*-anisidine, isopropylamine, *tert*-butylamine, di-*n*-butylamine, *N*-hydroxyethylpiperazine, bis-β,β'-cyanoethylamine, 4-aminobiphenyl, urea, DL-serine and ethylenediamine. With guanidine, the oxetane (XI) discussed below was obtained.

Dehydrogenation of 16-piperidinomethylyohimbol (VIII) with palladium in the presence of maleic acid gave the tetradehydro compound (IX) isolated as the diperchlorate.



Attempted alkylation of benzyl mercaptan and *n*-octyl mercaptan by I was unsuccessful.

The behavior of I when subjected to acid or basic hydrolytic conditions is worthy of comment. Acid hydrolysis of I resulted in the regeneration of yohimbyl alcohol. However, under basic conditions the product isolated furnished analytical data corresponding to those demanded by yohimbyl alcohol minus one molecule of water. Such a substance can arise by an elimination reaction followed by isomerization to give a 17-hydroxy-16-methyl yohimbene, possibly X, or by an intramolecular alkylation of the 17-hydroxyl group to give an oxetane (XI).



Structure X was ruled out on the basis of several observations. The infrared spectrum lacked the usual hydroxyl absorption at 2.85μ and showed only a broad band in the N—H region at 3.12μ. Oxidation of the substance by the Oppenauer method, by "manganese dioxide B",[11] by chromium trioxide-pyridine complex[12] and by other methods failed to yield the expected α,β-unsaturated ketone on the assumption that the C-17 hydroxyl function was still intact. Catalytic hydrogenation under moderately severe conditions (1000 p.s.i.g. and 100° over nickel) failed to detect a double bond.

Presence of an oxetane ring was suggested by infrared absorption at 10.2μ, although reliance on this evidence alone is rather risky in this case.[13,14] However, reduction of XI with lithium aluminum hydride in tetrahydrofuran for 48 hr. resulted in cleavage of the oxetane ring with the formation of 16-methylyohimbol (XII). This provides conclusive evidence for assignment of structure XI to the compound. Cleavage of the ring in this fashion substantiates the generalization of Searles that rupture of an oxetane ring occurs between oxygen and the least substituted carbon atom.[15] With the C-17 hydroxyl group now open, no difficulty in oxidation of 16-methylyohimbol to 16-methylyohimbone (XIII) was experienced. Finally, formation of the oxetane ring furnishes additional confirmation of the *cis* relationship of the carbomethoxyl group at C-16 and the C-17 hydroxyl group of yohimbine.

Acetolysis of XI resulted in the formation of a monoacetate of yohimbyl alcohol for which structure XIV is preferred, although the isomeric 17-acetoxy derivative of yohimbyl alcohol cannot be excluded.

Results of pharmacological tests of the various compounds described will be reported elsewhere.

EXPERIMENTAL[16,17]

Ethers of yohimbyl alcohol and their derivatives. The preparation of the isoamyl ether and its derivatives will be given in detail. The other compounds were prepared in a similar fashion. Pertinent data are given in Tables I and II for all substances.

A. *Yohimbyl alcohol isoamyl ether p-toluenesulfonate.* A solution of 15.3 g. of the *p*-toluenesulfonic acid ester of yohimbyl alcohol in 200 ml. of isoamyl alcohol was heated under reflux for 12 hr. The excess solvent was removed under reduced pressure and the residue was recrystallized first from methanol-ether and then from methanol-acetone.

B. *Yohimbyl alcohol isoamyl ether.* A suspension of 6.17 g. of the above *p*-toluenesulfonate in 100 ml. of acetone was

(11) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

(12) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(13) G. M. Barrow and S. Searles, *J. Am. Chem. Soc.*, **75**, 1175 (1953).

(14) R. F. Zurcher and Hs. H. Gunthard, *Helv. Chim. Acta.*, **38**, 849 (1955).

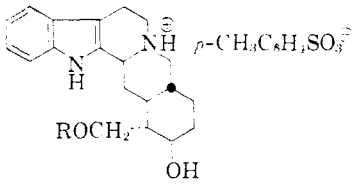
(15) S. Searles, K. A. Pollart and E. F. Lutz, *J. Am. Chem. Soc.*, **79**, 948 (1957).

(16) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(17) All melting points are uncorrected for stem exposure.

TABLE I

p-TOLUENESULFONIC ACID SALTS OF ETHERS OF YOHIMBYL ALCOHOL



R	Reflux Time	S[a]	Yield, %	M.P.[b]	$[\alpha]_D^{25}$[c]	Analysis: Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
iso-Amyl	12 hr.	A	54	280–281	+20.6°	67.6	7.8	4.9	67.3	7.9	5.0
2-Hexyl	4 days	A	58	269–270	+24.1°	68.0	8.0	4.8	68.1	7.8	5.0
2-Butyl	4 days	A	71	251–252	+21.0°	67.1	7.6	5.1	68.9	7.5	5.2
n-Octyl	4 hr.	A	47	263–264	+15.1°	68.8	8.2	4.6	68.9	8.2	4.6
iso-Propyl	5 days	B	54	258–259	+22.1°	66.6	7.4	5.2	66.8	7.1	4.9
4-Heptyl	4 hr.	A	64	272–273	+11.0°	68.4	8.1	4.7	68.2	8.4	4.4
Ethyl	6 days	B	61	279–280	+16.0°	66.1	7.3	5.3	66.4	7.1	5.3

[a] Solvent for recrystallization. A = methanol-ether; B = ethanol-ether. [b] M.p.'s taken in evacuated sealed capillaries. [c] Rotations taken in pyridine.

made basic with 10% sodium hydroxide solution and warmed on the steam bath until solution was complete. After removal of the solvent under reduced pressure, the residue was recrystallized from dilute acetone.

C. *Yohimbyl alcohol isoamyl ether methiodide.* One g. of iodomethane was added to solution of 0.5 g. of yohimbyl alcohol isoamyl ether in 5 ml. of acetone. A white precipitate formed immediately. After standing 12 hr. at room temperature, anhydrous ether was added to the mixture, the solid was collected and washed with ether. After recrystallization from methanol, the methiodide melted at 273–274°. $[\alpha]_D^{25}$ +8.76° (*c.* = 0.0095 in 75% pyridine).

Anal. Calcd. for $C_{25}H_{36}N_2O_2 \cdot CH_3I$: C, 58.0; H, 7.3; N, 5.2. Found: C, 57.8; H, 7.3; N, 5.4.

Yohimbyl alcohol isoamyl ether hydrochloride. A solution of 0.1 g. of yohimbyl alcohol isoamyl ether in 25 ml. of benzene was concentrated to 5 ml. After addition of 25 ml. of methanol, the solution was saturated with dry hydrogen chloride and concentrated. Addition of 10 ml. of anhydrous ether precipitated the hydrochloride which was recrystallized twice from methanol-ether and twice from ethanol-ether. $[\alpha]_D^{25}$ +24.4° (*c.* = 0.0074 in 45% ethanol).

Anal. Calcd. for $C_{25}H_{36}N_2O_2 \cdot HCl$: C, 69.3; H, 8.8; N, 6.5. Found: C, 69.2; H, 8.4; N, 6.8.

N-Ethylpiperidine. To a solution of 85.1 g. (1 mole) of piperidine in 100 ml. of absolute ethanol 119 g. (1.09 moles) of ethyl bromide was added over 1 hr. The solution was refluxed for 9 hr. After removal of the solvent under reduced pressure, the residue was taken up in water, the solution was made alkaline with sodium hydroxide and extracted with three 200 ml. portions of ether. Removal of the solvent from the dried ether extracts gave 68.4 g. (60.4%) of colorless liquid, b.p. 127.5–130°.

Anal. Calcd. for $C_7H_{15}N$: C, 74.3; H, 13.4; N, 12.4. Found: C, 74.3; H, 13.5; N, 12.4.

N-Ethylpiperidine p-toluenesulfonate. A solution of 1 g. of *N*-ethylpiperidine and 2 g. of *p*-toluenesulfonic acid monohydrate in 25 ml. of absolute ethanol was refluxed for 10 hr. After concentration to 10 ml. under reduced pressure dilution with 100 ml. of ether and cooling gave 2.38 g. of the salt. Recrystallization from methanol ether gave material, m.p. 139–141°.

Anal. Calcd. for $C_{14}H_{23}NO_3S$: C, 58.9; H, 8.1; N, 4.9. Found: C, 59.0; H, 8.1; N, 5.0.

N-Ethylpiperidine metho-p-toluenesulfonate. A solution of 2 g. of *N*-ethylpiperidine and 3.7 g. of methyl *p*-toluenesulfonate in 40 ml. of absolute ethanol was refluxed for 12 hr. and concentrated to dryness under reduced pressure. The reddish residual oil solidified on trituration with dry ether. Recrystallization from acetone with decolorizing carbon gave 1.71 g. of cubes, m.p. 87.8–89.8°, after drying over phosphorus pentoxide at 55° and 0.1 mm.

Anal. Calcd. for $C_{15}H_{25}NO_3S$: C, 60.2; H, 8.4; N, 4.7. Found: C, 60.3; H, 8.2; N, 4.6.

Yohimbyl alcohol p-toluenesulfonate. A solution of 0.5 g. of yohimbyl alcohol and 1 g. of *p*-toluenesulfonic acid monohydrate in 50 ml. of absolute ethanol was refluxed for 12 hr. White crystals, m.p. 294–297° (dec.), separated. After recrystallization from methanol-ether 0.46 g. of material, m.p. 291.5–294° (dec.), $[\alpha]_D^{25}$ +14.0° (*c.* = 0.076 in 80% ethanol), was obtained.

Anal. Calcd. for $C_{27}H_{34}N_2O_5S$: C, 65.0; H, 6.9; N, 5.6. Found: C, 64.9; H, 6.9; H, 5.7.

Yohimbyl alcohol metho-p-toluenesulfonate. A solution of 1.63 g. of yohimbyl alcohol and 1.02 g. of methyl *p*-toluenesulfonate in 30 ml. of absolute methanol was refluxed for 20 hr. and concentrated to dryness. Recrystallization twice from methanol-ether and once from ethanol gave 0.56 g. of white crystals, m.p. 258.5–261.2° (dec.), $[\alpha]_D^{25}$ +90.1° (*c.* = 0.0085 in 75% pyridine), $[\alpha]_D^{25}$ +77.5° (*c.* = 0.0092 in 80% ethanol).

Anal. Calcd. for $C_{28}H_{36}N_2O_5S$: C, 65.6; H, 7.1; N, 5.5. Found: C, 65.7; H, 7.2; N, 5.3.

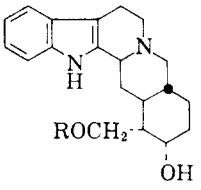
16-(n-Butylaminomethyl)yohimbol. A solution of 13.0 g. of the *p*-toluenesulfonic acid ester of yohimbyl alcohol in 100 ml. of *n*-butylamine was heated under reflux for 24 hr. After removal of most of the butylamine under reduced pressure, the residual thick sirup was poured into 500 ml. of water. The crude solid which separated was recrystallized three times from ethanol-acetone to give 2.8 g. (27%) of fine needles hydrated with one molecule of water of crystallization which was held very tenaciously. Pertinent data for this and the following compounds are given in Table III.

16-(1-Piperidinomethyl)yohimbol. This was prepared by the procedure used for the butylamino derivative. The crude solid was dissolved in methanol and the amine was isolated as the perchlorate. Recrystallization of the perchlorate from nitrobenzene gave 4.7 g. (28%) of colorless cubes. The salt retained 2.5 waters of crystallization.

16-(1-Piperidinomethyl)tetradehydroyohimbol. A solution of 1.25 g. of the above perchlorate and 1.16 g. of maleic acid in 40 ml. of hot 25% acetic acid was refluxed with 0.63 g. of palladium black for 5.5 hr. After filtration from the catalyst, the solution deposited a yellow solid on cooling.

TABLE II

ETHERS OF YOHIMBYL ALCOHOL

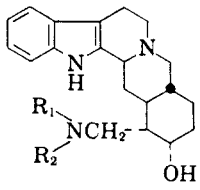


R	Yield, %	M.P.[a]	$[\alpha]_D^{25}$[b]	Analysis Calcd. C	H	N	Found C	H	N
iso-Amyl[c]	76	100–102	+2.95°	72.4	9.2	6.8	72.1	9.0	6.9
iso-Amyl[d]	..	160–161	+2.5°	75.7	9.1	7.1	75.4	8.9	7.4
2-Hexyl	35	140–141	+17.2°	76.1	9.3	6.8	76.3	9.3	6.6
2-Butyl	74	142–143	+10.3°	75.3	9.0	7.3	75.3	8.9	7.0
n-Octyl	71	177–179	+9.3°	76.7	9.6	6.4	76.7	9.4	6.2
iso-Propyl	56	188–189	+12.7°	75.0	8.8	7.6	74.9	8.7	7.4
4-Heptyl	71	165–167	+6.0°	76.4	9.5	6.6	76.5	9.2	6.4
Ethyl	65	196–198	+4.9°	74.5	8.5	7.9	74.3	8.8	7.6

[a] M.p.'s taken in evacuated sealed capillaries. [b] Rotations taken in pyridine. [c] This is a monohydrate. Dried *in vacuo* at room temperature. [d] Anhydrous compound. Dried at 100° and 0.3 mm. for 12 hrs.

TABLE III

16-AMINOMETHYL DERIVATIVES OF YOHIMBOL



R_1	R_2	M.P.	$[\alpha]_D^{25}$[a]	Analysis Calcd. C	H	N	Found C	H	N
n-Butyl	H	160–162 (dec.)	+42.8	72.0	9.3	10.5[b]	71.6	9.1	10.4
1-Piperidino		320–324 (dec.)	+14.6	48.2	6.7	6.7[c]	48.3	6.2	6.8
Cyclohexyl	H	161–163 (dec.)	+9.9	73.4	9.2	9.8	73.1	9.1	9.4
Benzyl	H	186–187 (dec.)	+25.0	74.7	8.1	9.7[b]	74.4	8.0	9.6
4-Diethylamino-1-methylbutylamino	H	126–127 (dec.)	+69.0	69.2	9.9	11.1[d]	69.2	9.8	11.3

[a] Rotations taken in pyridine. [b] Calculated as the monohydrate. [c] Calculated as $C_{25}H_{35}N_3O \cdot 2HClO_4 \cdot 2.5H_2O$. [d] Calculated as the dihydrate.

Recrystallization from dilute methanol gave 400 mg. (34%) of the diperchlorate monohydrate, m.p. 308° (dec.), $[\alpha]_D^{27}$ +114.0° (pyridine).

Anal. Calcd. for $C_{25}H_{31}N_3O \cdot 2HClO_4 \cdot H_2O$: C, 50.6; H, 5.9; N, 7.1. Found: C, 50.8; H, 6.0; N, 7.1.

16-Cyclohexylaminomethylyohimbol. A solution of 11 g. of the *p*-toluenesulfonic acid ester of yohimbyl alcohol in 100 ml. of cyclohexylamine was heated in an oil bath at 104° for 9 hr. On cooling 3.8 g. (61%) of the *p*-toluenesulfonic acid salt of cyclohexylamine separated as broad plates. The filtrate from the salt was evaporated to dryness. After extraction of water soluble amine salts by trituration with water, the dried residue was dissolved in the minimum amount of benzene and chromatographed over 200 g. of alumina. A bright yellow band which was eluted with 3:2 benzene-chloroform represented the major component of the crude mixture. Removal of the solvent left a dark solid which was recrystallized from acetone to give 133 mg. (1.42%) of product as the monohydrate.

16-Benzylaminomethylyohimbol. A solution of 7.8 g. of I in 75 ml. of benzylamine was heated in an oil bath at 121° for 22 hr. After partial removal of the solvent under reduced pressure, the thick oil was poured into 250 ml. of water. The crude solid which separated was recrystallized several times from benzene-chloroform to give 4.55 g. (67%) of product as the monohydrate.

16-(4-Diethylamino-1-methylbutylamino)yohimbol. A solution of 16.7 g. of I in 150 ml. of 1-diethylamino-4-aminopentane was heated in an oil bath at 125° for 4 hr. and poured into 1 l. of water. The crude yellow solid (12.0 g.) which separated was dissolved in 300 ml. of benzene and chromatographed over 300 g. of alumina with 3:1 benzene-chloroform as eluent. Removal of the solvent from the eluate left a red gum which crystallized as needles from dilute ethanol. Further crystallization gave 2.10 g. (12.9%) of the product as the dihydrate.

The oxetane (XI). A solution of 4.0 g. of I in 145 ml. of 66% ethanol containing a molar equivalent of sodium hy-

droxide was refluxed for 4 hr. On cooling, colorless needles separated. These were collected, washed well with water, and recrystallized from 66% ethanol to give 2.3 g. (90%) of the oxetane (XI), m.p. 252° (dec.), $[\alpha]_D^{27}$ +37.8° (pyridine).

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.8; H, 7.9; N, 9.1. Found: C, 77.7; H, 7.9; N, 9.0.

When alkylation of guanidine with I was attempted, the oxetane (XI) was the only product isolated. A solution containing guanidine was prepared by adding 8.0 g. (0.2 mole) of sodium hydroxide to a solution of 28.6 g. (0.32 mole) of guanidine hydrochloride in 200 ml. of 66% ethanol. To this was added 4.0 g. of I and the solution was refluxed for 4.5 hr. On cooling, long colorless needles of the oxetane separated (50% yield). Identification was by m.p., specific rotation and infrared.

Acetoylsis of the oxetane (XI). A solution of 2.2 g. of XI in 25 ml. of glacial acetic acid and 20 ml. of acetic anhydride was refluxed for 1 hr. and the solvents were removed under reduced pressure. The residue was slurried with water, made basic with ammonium hydroxide and the insoluble material was collected, washed well with water, and crystallized twice from 66% ethanol to give 0.76 g. (30%) of 16-methyl-17-acetoxyyohimbane or 16-acetoxymethylyohimbol, m.p. 187–189°, $[\alpha]_D^{27}$ −42.5° (pyridine). The infrared spectrum taken as a Nujol mull showed a sharp peak at 5.80μ with a shoulder at 5.90μ.

Anal. Calcd. for $C_{22}H_{28}N_2O_2$: C, 75.0; H, 8.0; N, 7.9. Found: C, 74.8; H, 7.9; N, 7.5.

16-Methylyohimbol (XII). A. *From the p-toluenesulfonic acid ester of yohimbyl alcohol.* To a mixture of 2.0 g. of lithium aluminum hydride in 40 ml. of dry tetrahydrofuran, a solution of 4.60 g. of I in 120 ml. of tetrahydrofuran was added dropwise with stirring. After the addition, the mixture was refluxed for 4.5 hr. After careful addition of water refluxing was continued for an additional hr. The supernatant liquid was decanted from the inorganic salts and concentrated under reduced pressure. The solid which separated was crystallized from 66% ethanol to give 1.87 g. (63%) of 16-methylyohimbol, m.p. 235° (dec.), $[\alpha]_D^{27}$ −20.4° (pyridine). The infrared spectrum was identical with that of a known sample.[18]

Anal. Calcd. for $C_{20}H_{26}N_2 \cdot {}^1/_2H_2O$: C, 75.2; H, 8.5; N, 8.8. Found: C, 75.0; H, 8.6; N, 8.8.

B. *From the oxetane* (XI). When XI (1.1 g.) was refluxed with lithium aluminum hydride (1.0 g.) in 150 ml. of tetrahydrofuran for 46 hr., 16-methylyohimbol was obtained in 27% yield. Identification was by infrared, m.p., and specific rotation.

16-Methylyohimbone (XIII). A mixture of 1.0 g. of 16-methylyohimbol, 10 g. of aluminum isopropoxide, 50 ml. of dry xylene, and 100 ml. of dry acetone was refluxed for 24 hr. After removal of the acetone under reduced pressure, the xylene solution was extracted with 2*N* sulfuric acid. The acid extract was made strongly basic with sodium hydroxide. The dried precipitate (0.83 g.), m.p. 286° (dec.) was dissolved in benzene and chromatographed over alumina. Elution with 1:1 benzene-chloroform gave 60 mg. of colorless needles, m.p. 293° (dec.), $[\alpha]_D^{27}$ −88° (pyridine). The infrared spectrum, taken as a Nujol mull, showed one band in the carbonyl region at 5.85μ.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.9; H, 7.9; N, 9.1. Found: C, 78.0; H, 8.1; N, 9.0.

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(18) We wish to express our appreciation to Professor Paul Karrer for providing a sample of 16-methylyohimbol for comparison.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Physiologically Active Compounds. III. Hydrochlorides of Amino Esters of Phenylcyclohexylglycolic Acids, of Amides of Benzilic, Phenylcyclohexyl- and Dicyclohexylglycolic, and Phenylcyclohexylacetic Acids; 2-Methylthioethyl Ester Methiodides of Substituted Benzilic Acids

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Fourteen amino ester hydrochlorides of glycolic acids, eight amino ester hydrochlorides of acid amides, and three methyl iodides of thioalkyl esters of substituted benzilic acids have been prepared. In the physiological tests reported, two compounds appear to be more active in experimental animals than atropine in preventing mortality from an anticholinesterase compound; four exhibit pronounced anticholinergic activity, and one, antihistaminic activity. In the cerebral stimulation test, one compound appears to be more active than benactyzine, a commercial product, although it possesses five times the atropine-like activity.

This paper reports a continuation[3] of the syntheses and tests for physiological activity of compounds related to the amino esters of benzilic acids. The ester hydrochlorides of the phenylcyclohexylglycolic acids, which are listed in Table I, were prepared mostly by the partial hydrogenation of the proper benzilic acid derivatives. Since in most of these cases only one of the phenyl groups in the benzilic acid moiety was substituted, it was necessary to determine which of the rings present was hydrogenated. In two cases studied, the 4-methyl- and 3,5-dimethylbenzilic acid derivatives, it was shown that the unsubstituted ring was attacked. Evidence in support of this contention was twofold: (1) An examination of the ultraviolet absorption curves of the half-hydrogenated products given in Fig. 1. It will be observed that (a) the principal

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