TABLE II

Compound	Yield, %	B.p., °C.	M.p., °C.	$n^{25}D$	d^{25}_4	Analyses, %[a] Theory C	Found C	Theory H	Found H
$CF_3COOC_6H_5$	95	146.5–147.0	− 8.5	1.4183	1.276	50.54	51.00	2.65	2.49
$C_2F_5COOC_6H_5$	94	153.0–153.5	−23.0	1.4078	1.324	45.01	45.26	2.10	2.03
$C_3F_7COOC_6H_5$	96	162.5–163.0	−27.0	1.4156	1.350	41.39	41.42	1.74	1.69
$C_4F_9COOC_6H_5$	92	179–180	−25.0	1.3888	1.438	38.84	39.00	1.48	1.47
$C_5F_{11}COOC_6H_5$	95	196–197	−18.0	1.3715	1.533	36.94	36.81	1.29	1.18

[a] Analyses by Clark Microanalytical Lab., Urbana, Illinois.

Company for part of the work reported in this paper.

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Cholylamine Esters

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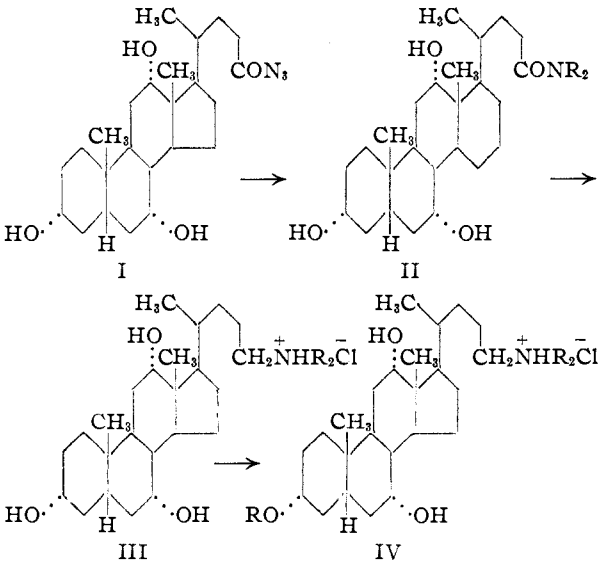
Liliaceous plants of the *Veratrum* and *Zygadenus* genera[1] contain various ester alkaloids that have been employed with some success in the treatment of hypertension. The most potent members of the group, germitrine, neogermitrine and protoveratrine are esters of C_{27}-polyhydroxy tertiary amines of probably steroidal character. Although the problem of structure elucidation is still far from solved, it seemed of interest to see if simpler synthetic compounds corresponding roughly to the known specifications of the natural hypotensive agents would exhibit comparable physiological properties.

Methyl cholate was converted through cholic acid hydrazide to the azide[2] I, which has been shown to condense with piperidine and with dimethylamine to give the corresponding amides[3] II; we effected condensation also with morpholine and with diethylamine. Reduction of the amides with lithium aluminum hydride gave tertiary amines that were isolated as the hydrochlorides III. Partial acylation of the free bases afforded 3-cathyl, 3-acetyl and 3-veratroyl esters of the tertiary steroidal bases, purified as the hydrochlorides IV. In tests for hypotensive activity in dogs kindly carried out by Dr. George L. Maison of the Department of Pharmacology, Boston University School of Medicine through the courtesy of Riker Laboratories, Inc., the following compounds gave completely negative results: cholylpiperidine and its 3-veratrate; the hydrochlorides of cholylpiperidine 3-veratrate and 3-acetate; N,N-dimethylcholylamine.[4]



R = $CO_2C_2H_5$, $COCH_3$, $COC_6H_3(OCH_3)_2$-3,4

Experimental

Cholic Acid Hydrazide.—A mixture of 8.7 g. of methyl cholate (m.p. 153–154°) and 4.8 g. of 85% hydrazine hydrate was moistened with a few cc. of ethanol and heated on the steam-bath under reflux for 60 hr. The cooled reaction mixture was triturated with a little ethanol and the solid product was collected and washed with ethanol; first crop: 2.35 g., m.p. 186–187°, α_D +34.3° MeOH (*c* 3.41), λ^{Di} 2.92, 3.06, 5.93, 6.08 μ (m.p. reported[2] 188–189°). Evaporation of the mother liquor and crystallization of the residue from water afforded 4.0 g. more of white needles m.p. 186–188° (total yield 6.35 g., 73%). Condensation of methyl cholate (36 g.) with anhydrous hydrazine (8 g.) in the same way afforded 31.7 g. (88%) of cholic acid hydrazide, m.p. 183–186°.

Cholic Acid Piperidide (II).—A solution of 4.3 g. of cholic acid hydrazide in 100 cc. of water and 10 cc. of 1 *N* hydrochloric acid was stirred mechanically in an ice-bath during dropwise addition of 10 cc. of 1 *N* sodium nitrite solution. The resulting flocculent precipitate of cholic acid azide was let stand for 15 min.; then 1.8 g. of piperidine was added and the mixture shaken mechanically for 24 hr. The resulting crude piperidide, filtered, washed and dried, melted at 234–239°, yield 3.0 g. (62%). Several recrystallizations from aqueous methanol raised the m.p. to 243–246° (reported[3] 246°), α_D +31° MeOH (*c* 1.61), +33.4° Py (*c* 3.17), λ^{Chf} 2.95, 6.10 μ.

N-Cholylpiperidine Hydrochloride (III).—A solution of 2.8 g. of cholic acid piperidide in 25 cc. of tetrahydrofuran was refluxed for 3 hr. with 1 g. of lithium aluminum hydride and the mixture was let stand overnight and then treated with aqueous sodium sulfate solution (gelatinous precipitate) and aqueous alkali and extracted with ether. Addition of 36% hydrochloric acid to the dried ethereal solution precipitated the amine hydrochloride, which crystallized from ether in fine needles (2.1 g., 72%), m.p. 298–299° dec., α_D +32° MeOH (*c* 3.96).

Anal. Calcd. for $C_{29}H_{52}O_3NCl$ (498.17): C, 69.91; H, 10.52. Found: C, 70.16; H, 10.27.

The free base (amorphous) showed no carbonyl infrared absorption.

Esters. (a) 3-Cathylate (IV).—A solution of 1 cc. of ethyl chlorocarbonate in 3 cc. of dioxane was added dropwise with ice cooling to a solution in 2 cc. of pyridine of the

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(2) S. Bondi and E. Miller, *Z. physiol. Chem.*, **47**, 499 (1906).

(3) W. Borsche and A. Schwarz, *Ber.*, **60**, 1843 (1927).

(4) Method of assay: G. L. Maison, E. Gotz and J. W. Stutzman *J. Pharmacol.*, **103**, 74 (1951).

amorphous base from 1 g. of N-cholylpiperidine hydrochloride. After standing for 16 hr. the solution was diluted with water, neutralized with solid sodium bicarbonate solution, and extracted with ether. The dried solution was evaporated at reduced pressure and the residue further dried by addition of benzene and evaporation. Conversion to the hydrochloride and crystallization from methanol-ether gave 0.4 g. (35%) of pure salt, m.p. 269–270° dec., α_D +46° MeOH (*c* 2.55), λ^{Chf} 2.93, 4.1–4.2, 5.76 μ.

Anal. Calcd. for $C_{32}H_{56}O_5NCl$ (570.23): C, 67.38; H, 9.90. Found: C, 67.33; H, 9.87.

(b) **3-Acetate.**—The base from 1 g. of N-cholylpiperidine hydrochloride was treated in 10 cc. of dioxane with 4 cc. of pyridine and 6 cc. of acetic anhydride for 48 hr. at 20° and the product isolated as the hydrochloride, which was crystallized from methanol-ether; m.p. 249–252°, α_D +29° MeOH (*c* 2.56), λ^{Chf} 3.0, 4.2, 5.8 μ.

Anal. Calcd. for $C_{31}H_{54}O_4NCl$ (540.21): C, 68.92; H, 10.08. Found: C, 69.02; H, 10.30.

(c) **3-Veratrate.**—A solution of the cholylpiperidine from 0.85 g. of hydrochloride in 7 cc. of dioxane was treated with a solution in 4 cc. of dioxane and 3 cc. of pyridine with 2 g. of veratroyl chloride, prepared according to Kostanecki and Tambor[5] and crystallized from benzene–petroleum ether (m.p. 70–71°). After standing for 36 hr. in a refrigerator the mixture was worked up and the product crystallized as the hydrochloride from methanol–ether; m.p. 261° dec., α_D +43° MeOH (*c* 2.82), λ^{Chf} 2.96, 4.1–4.2, 5.9, 6.2 μ.

Anal. Calcd. for $C_{38}H_{60}O_6NCl$ (662.33): C, 68.91; H, 9.13. Found: C, 68.79; H, 9.54.

Cholic Acid Morpholide.—By the procedure given above, 2.15 g. of cholic acid hydrazide afforded 2.0 g. (82%) of crude product, m.p. 266–268°. Recrystallization from chloroform–methanol raised the m.p. to 273–275° dec., α_D +34° Py (*c* 1.92), λ^{Chf} 3.0, 6.1 μ.

Anal. Calcd. for $C_{28}H_{47}O_5N$ (477.67): C, 70.40; H, 9.92. Found: C, 70.44; H, 10.09.

N-Cholylmorpholine Hydrochloride.—This salt was obtained as the monohydrate in 46% yield by reduction of the above amide with lithium aluminum hydride and crystallization as hydrochloride; m.p. 289–290°, α_D −32° MeOH (*c* 2.20).

Anal. Calcd. for $C_{28}H_{50}O_4NCl \cdot H_2O$ (518.16): C, 64.90; H, 10.12. Found: C, 64.66, 65.07; H, 10.08, 10.37.

N-(3-Cathylcholyl)-morpholine hydrochloride melted at 235–238° dec., α_D +51° MeOH (*c* 0.36), λ^{Chf} 2.95, 4.3, 5.76 μ.

Anal. Calcd. for $C_{31}H_{54}O_6NCl$ (572.20): C, 65.06; H, 9.51. Found: C, 64.79; H, 9.35.

N,N-Dimethylcholylamine Hydrochloride.—N,N-Dimethylcholic acid amide was obtained by the general procedure described in 90% yield, m.p. 168–172° dec. (reported 170–171°,[6] 179°[3]), α_D +36° MeOH (*c* 2.56), λ^{Chf} 2.95, 6.12 μ. Reduction of 1.8 g. of amide with excess lithium aluminum hydride gave 1.53 g. (81%) of the amine hydrochloride, m.p. 280–281°, α_D +33° MeOH (*c* 2.24).

Anal. Calcd. for $C_{26}H_{48}O_3NCl$ (458.11): C, 68.18; H, 10.56. Found: C, 67.94; H, 10.43.

3-Cathyl-N,N-dimethylcholylamine hydrochloride melted at 242–243°, α_D +52° MeOH (*c* 1.76), λ^{Chf} 3.0, 4.2–4.4, 5.78 μ.

Anal. Calcd. for $C_{29}H_{52}O_5NCl$ (530.17): C, 65.69; H, 9.89. Found: C, 65.47; H, 9.89.

N,N-Diethylcholic Acid Amide.—The crude product, m.p. 115–120° (81% yield), separated very slowly from aqueous acetone to give very hygroscopic crystals of the monohydrate, m.p. 118–121°, α_D +35° MeOH (*c* 3.32), λ^{Chf} 2.95, 6.12 μ.

Anal. Calcd. for $C_{28}H_{49}O_4N \cdot H_2O$ (481.70): C, 69.81; H, 10.67. Found: C, 69.90; H, 10.27.

N,N-Diethylcholylamine hydrochloride, obtained in 51% yield by reduction of the crude amide (m.p. 115–120°), melted at 247–248°, α_D +33° MeOH (*c* 2.92).

Anal. Calcd. for $C_{28}H_{52}O_3NCl$ (486.17): C, 69.17; H, 10.78. Found: C, 69.24; H, 10.98.

(5) St. v. Kostanecki and J. Tambor, *Ber.*, **39**, 4022 (1906).

(6) P. Mylius, *Ber.*, **20**, 1968 (1887).

3-Cathyl-N,N-diethylcholylamine hydrochloride melted at 214–216°, α_D +47.5° MeOH (*c* 2.44), λ^{Chf} 3.0, 4.2, 5.76 μ.

Anal. Calcd. for $C_{31}H_{56}O_5NCl$ (558.23): C, 66.69; H, 10.11. Found: C, 66.97; H, 10.37.

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2-Hydroxy-4-aminobenzenephosphonic Acid, an Analog of *p*-Aminosalicylic Acid

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A series of phosphonic and phosphinic acids prepared in this Laboratory have been tested for antibacterial action *in vitro*.[1] Although a number of them have been found to possess some activity, only phosphanilic acid approached in potency such known antibacterial agents as sulfathiazole. The synthesis of compounds related to phosphanilic acid would appear desirable. We are reporting here the preparation of 2-hydroxy-4-aminobenzenephosphonic acid. This compound was of special interest because of its similarity to *p*-aminosalicylic acid (PAS), a well-known antitubercular agent.

The synthesis was accomplished starting with 2-methoxy-4-nitrobenzenephosphonic acid[2] which was demethylated to 2-hydroxy-4-nitrobenzenephosphonic acid; the latter was then reduced to the desired amino compound. The demethylation was performed by refluxing the methoxy compound in 40% hydrobromic acid for 28 hours. A shorter reflux time gave some unchanged starting material, while in more concentrated hydrobromic acid (48%) phosphorus was cleaved from the ring. 2-Hydroxy-4-nitrobenzenephosphonic acid was isolated from the hydrobromic acid solution and purified by recrystallization. The yields were somewhat low due to the solubility of the impure compound in both aqueous and organic solvents.

When an attempt was made to reduce 2-hydroxy-4-nitrobenzenephosphonic acid with Raney nickel and hydrogen at *p*H 6, we found that phosphorus was again cleaved from the ring; both *m*-aminophenol and phosphoric acid (as magnesium ammonium phosphate) were recovered from the filtrate. In contrast 2-methoxy-4-nitrobenzenephosphonic acid was readily reduced to the corresponding amino compound by the use of Raney nickel.

The reduction of the hydroxy compound was accomplished by the use of Adams platinum oxide catalyst and 10% hydrochloric acid as the solvent. Because of the poor yields in the isolation of the 2-hydroxy-4-nitrobenzenephosphonic acid, an attempt was made to reduce the hemi-potassium salt.[3] This salt, which is an intermediate in the isolation procedure, is much less soluble than the free acid. Unfortunately sufficient potassium bromide was occluded when this salt was isolated to dissolve the platinum oxide in acid solution and prevent reduction.

(1) J. D. Thayer, H. J. Magnuson and M. S. Gravatt, *Antibiotics & Chemotherapy*, **3**, 256 (1953).

(2) L. D. Freedman, H. Tauber, G. O. Doak and H. J. Magnuson, THIS JOURNAL, **75**, 1379 (1953).

(3) G. O. Doak and L. D. Freedman, *ibid.*, **73**, 5658 (1951).