TABLE I

ARYLOXACETONES

Phenoxyacetones	Yield,[a] %	M.p., °C.	Formula	Analyses,[c] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	*A. niger* inhibition, % at 250 p.p.m.
Cl_5	94.5	106.5–107	$C_9H_5O_2Cl_5$	33.53	33.67	1.56	1.57	72
2,4-Cl_2	15.5[b]	55.5–56.5	$C_9H_8O_2Cl_2$	49.35	49.40	3.68	3.84	84
2-CH_3-3,4,5,6-Br_4	84[b]	149.5–150.5	$C_{10}H_8O_2Br_4$	25.03	25.35	1.68	2.01	17
2-Br-4-C_6H_5	24[b]	88.5–89	$C_{15}H_{13}O_2Br$	59.05	59.07	4.26	4.54	15
4-$C_6H_5CH_2O$	70	73.5–75	$C_{16}H_{16}O_3$	74.97	75.24	6.29	6.57	17
Naphthoxyacetones								
1-Br-2	97	69.5–70.5	$C_{13}H_{11}O_2Br$	55.93	56.19	3.97	3.91	
1,6-Br_2-2	95	109.5–110.5	$C_{13}H_{11}O_2Br$	(Br Calcd.: 28.63.		Found: 28.58)		6
1,6-Br_2-2	90	151.5–152.5	$C_{13}H_{10}O_2Br_2$	43.61	43.72	2.81	3.07	0
2,4-Cl_2-1	94	87–88	$C_{13}H_{10}O_2Cl_2$	58.02	58.06	3.75	3.82	0

[a] All yields are for products with melting points not more than two degrees below that of the analytical sample. [b] No potassium iodide added. [c] Analyses by Clark Microtechnical Laboratories.

oxyketones. Most of these ketones were prepared by the Hurd and Perletz[2] modification of the method of Bradsher and Rosher.[3] Fungistatic action of the compounds against *Aspergillus niger* was determined essentially as described by Leonard and Blackford,[4,5] and as may be seen from Table I none of the aryloxyacetones completely inhibited growth of the fungus at 250 parts per million.

1-(6-Bromo-2-naphthoxy)-2-hexanone was prepared from 1-chloro-2-hexanone[6] by the same general procedure, yielding white flakes from alcohol, m. p. 67–68° (48% yield). The analytical sample melted at 68.5–69°. At 250 p.p.m. it inhibited the growth of *A. niger* by only 23%.

Anal. Calcd. for $C_{16}H_{17}O_2Br$: C, 59.82; H, 5.34. Found: C, 59.46; H, 5.65.

(2) C. D. Hurd and P. Perletz, THIS JOURNAL, **68**, 38 (1946).
(3) C. K. Bradsher and R. Rosher, *ibid.*, **61**, 1524 (1939).
(4) J. M. Leonard and V. L. Blackford, *J. Bact.*, **57**, 339 (1949).
(5) We are indebted to Mrs. Rita S. Kardon and Mrs. Barbara Bayless for carrying out these tests.
(6) J. Cason, THIS JOURNAL, **68**, 2078 (1946).

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Aromatic Esters of Fluorocarbon Acids

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A series of aromatic esters of fluorocarbon acids were prepared and their physical properties studied.

Several reactions were attempted in order to prepare these compounds; however, only one gave favorable results.

The reactions and yields in the case of trifluoroacetic acid were

$$C_6H_5ONa + CF_3COCl \longrightarrow CF_3COOC_6H + NaCl \quad 20\% \text{ yield}$$

$$C_6H_5OH + CF_3COOH \xrightarrow{H_2SO_4} \text{N.R.}$$

$$C_6H_5OH + \text{excess } CF_3COOH \longrightarrow CF_3COOC_6H_5 + CF_3COOH\cdot H_2O\ (1)\ (\text{azeotrope}) \quad 15\% \text{ yield}$$

$$C_6H_5OH + (CF_3CO)_2O \longrightarrow CF_3COOC_6H_5 + CF_3COOH \quad 95\% \text{ yield}$$

(1) Swarts, *Bull. soc. chim. Belg.*, **48**, 176 (1939); *C. A.*, **33**, 8172 (1939).

The esters were soluble in ethyl ether, ethyl alcohol, benzene and dibutforyl oxide. The esters were found slightly soluble in water, 50% sulfuric acid, 10% sodium bicarbonate and concentrated sulfuric acid, after standing a period of two weeks. With 10% sodium hydroxide they underwent saponification. The solubility and rate of saponification decreased proportionally from phenyl trifluoroacetate to phenyl caproforate.

Experimental

Preparation of Anhydrides.—The anhydrides used in the preparation of the esters were prepared by heating the corresponding acid with phosphorus pentoxide. The physical properties of the anhydrides are listed in Table I.

TABLE I

Compound	B.p., °C.	$n^{25}D$	d^{25}_4	F Analyses, % Theory	F Found
$(CF_3CO)_2O$[1]	39.5–40.5	1.269	1.490	...	...
$(C_2F_5CO)_2O$	71.5–72.0	1.273	1.571	76.16	75.86
$(C_3F_7CO)_2O$[2]	107–107.5	1.285[a]	1.665[a]	...	...
$(C_4F_9CO)_2O$	137–137.5	....	....	67.05	66.78
$(C_5F_{11}CO)_2O$	175–176	1.295	1.769	68.51	68.38

[a] Determined at 20°.

Preparation of Esters.—The esters were prepared by adding the anhydrides dropwise to phenol, maintained at 120° with constant stirring. A slight excess of phenol was used with the anhydrides. The quantities of anhydrides taken were: $(CF_3CO)_2O$, $(C_2F_5CO)_2O$, $(C_3F_7CO)_2O$ (0.05 *M*) and $(C_4F_9CO)_2O$, $(C_5F_{11}CO)_2O$ (0.001 *M*).

The reaction products were then fractionated through a 50-cm. column, 8-mm. i.d. packed with $^1/_{16}$-inch glass helices. In the case of the preparation of phenyl valerforate, after the anhydride was added to the phenol, the reaction mixture was fractionated to remove valerforic acid and the residue washed three times with 50-ml. portions of hot water to remove phenol. The remaining ester was dried over anhydrous magnesium sulfate and fractionated. The yields obtained are listed in column 2 of Table II.

The authors wish to acknowledge the sponsorship of the Minnesota Mining and Manufacturing

(2) "Heptafluorobutyric Acid," Technical Bulletin, Minnesota Mining & Mfg. Co. (1949).

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.

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Cholylamine Esters

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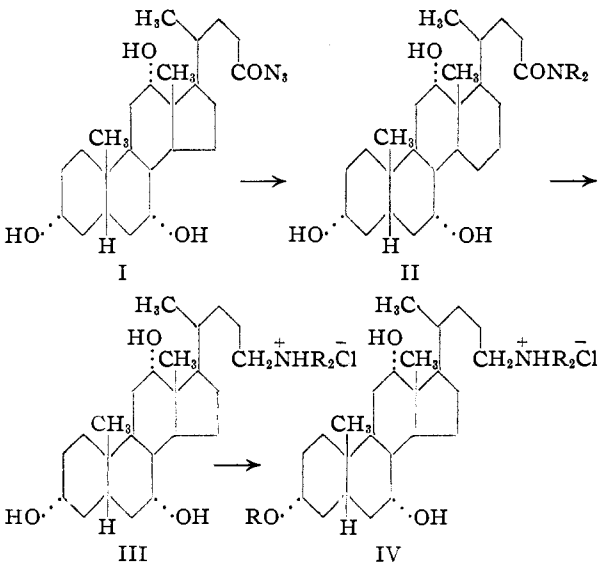
Liliaceous plants of the *Veratrum* and *Zygadenus* genera[1] contain various ester alkaloids that have been employed with some success in the treatment of hypertension. The most potent members of the group, germitrine, neogermitrine and protoveratrine are esters of C_{27}-polyhydroxy tertiary amines 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).