TABLE I

$RSCH_2CHCO_2CH_3$
$|$
$NHCOCF_3$

No.	R	Yield, %	Calcd, % C	H	N	S	Found, % C	H	N	S
3	Phthalimido–	65	44.68	2.95	7.45	8.52	44.66	2.99	7.54	8.57
4	$C_6H_5CH_2S$–	97	44.18	3.99	3.96	18.15	43.78	4.21	4.13	17.92
5	$HOOCCHCH_2S$– $\lvert$ $NH_3^+Cl^-$	99	27.94	3.65	7.24	16.58	28.24	4.17	7.33	16.89
6	Glu-Cy– $\lvert$ Gly	92	35.82	4.32	10.44	11.95	35.81	4.43	10.34	12.23

thetic route to unsymmetrical cysteine disulfides. The possibility of using thiophthalimides in peptide synthesis with selectively removable amino and carboxylic acid protective groups is being further explored.

Experimental Section

Melting points were taken on a Gallenkamp block and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 141 automatic polarimeter. Elemental analyses were performed by Organic Micro-analyses, Montreal. Infrared spectra were recorded on a Perkin-Elmer 257 grating spectrometer. Mass spectra were obtained on an AEI-MS-902 instrument. Nmr spectra were recorded on a Varian T-60 spectrometer.

***N*-Trifluoroacetyl-*S*-phthalimido-L-cysteine Methyl Ester (3).**—To a suspension of 4.60 g (0.01 mol) of disulfide **1** in 30 ml of 1,2-dichloroethane (DCE) at 0° was added 4.80 g (0.03 mol) of bromine in 15 ml of DCE. After stirring for 2–3 min, the cloudy, red solution was rapidly added to a similarly cooled suspension of 3.70 g (0.02 mol) of the potassium derivative of phthalimide in 45 ml of DCE. Anhydrous conditions were maintained throughout the experiment. After stirring at 0° for 10 min., the suspension was stirred for an additional 90 min at ambient temperature. Insoluble material was then filtered, giving 2.39 g (100%) of KBr. The filtrate was evaporated *in vacuo*, giving an orange solid, which on recrystallization from methanol–water gave 4.87 g (65%) of white needles mp 121–123°. A second recrystallization gave a sample of analytical purity: mp 125–126°; $[\alpha]^{22}D$ +54.4° (*c* 0.226, CCl_4); ir (KBr) 3260, 1730, 1690, 1540, 1270, 1180, 1150, 1040, cm^{-1}.

***N*-Trifluoroacetyl-*S*-benzylthio-L-cysteine Methyl Ester (4).**—A solution of 1.00 g (2.7 mmol) of **3** and 0.33 g (2.7 mmol) of benzyl mercaptan in 10 ml of ethyl acetate was refluxed for 24 hr. On subsequent cooling, phthalimide crystallized and was filtered. The solvent was removed *in vacuo* and the residue was taken up in 5 ml of carbon tetrachloride; additional phthalimide was obtained, total yield 0.38 g (96%), mp 234–235° (lit.[10] mp 238°). The filtrate was again evaporated *in vacuo*, giving a clear oil which crystallized on cooling to give 0.92 g (97%) of a pale yellow solid: mp 38–40°; $[\alpha]^{22}D$ +39.7° (*c* 0.363, $CHCl_3$); ir (KBr) 3300, 1740, 1700, 1540, 1300, 1200, 1180, 1160 cm^{-1}.

***N*-Trifluoroacetyl-*S*-cysteinyl-L-cysteine Methyl Ester Hydrochloride (5).**—A solution of 0.233 g (1.33 mmol) of L(+)-cysteine hydrochloride monohydrate[11] and 0.500 g (1.33 mmol) of **3** in 10 ml of ethanol was refluxed for 2 hr. On cooling, phthalimide crystallized and was filtered. The filtrate was evaporated to ~2–3 ml and 20 ml of water was added, giving an additional 0.006 g of phthalimide on cooling, total yield 0.179 g (91%), mp 234–237°. The filtrate was then evaporated *in vacuo* to give a white, solid foam, which was dried to constant weight under vacuum: yield 0.512 g (99%); mp 151–153° dec; $[\alpha]^{22}D$ −142.4° (*c* 0.433, 1 *N* HCl); ir (KBr) 3700–2400 (broad), 1800–1680, 1570, 1200 cm^{-1} (broad).

***N*-Trifluoroacetyl-*S*-glutathionyl-L-cysteine Methyl Ester (6).**—A solution of 0.408 g (1.33 mmol) of glutathione and 0.500 g (1.33 mmol) of **3** in 20 ml of ethanol–water (50:50 v/v) was refluxed for 2 hr. After cooling to room temperature and standing for 8 hr, 0.187 g (95%) of phthalimide crystallized and was filtered, mp 228–232°. The solvent was evaporated *in vacuo* to 10 ml and 10 ml of water were added. On cooling overnight, an additional 0.049 g of precipitate formed. Tlc [silica gel, C_6H_6–Et_2O (5:2)] showed this second crop to be composed of phthalimide and the symmetrical disulfide **1**. The filtrate was evaporated *in vacuo* and dried to constant weight, giving 0.659 g (92%) of a white, solid foam: mp 173° dec; $[\alpha]^{22}D$ −103.0° (*c* 0.463, 1 *N* HCl); ir (KBr) 3700–2400 (broad), 1720, 1650, 1540, 1200 cm^{-1} (broad). Tlc [cellulose, BuOH–HOAc–H_2O (12:3:5)] showed the presence of a trace impurity of lower mobility than **6** attributable to a small quantity of the symmetrical glutathione disulfide.

Hydrolysis of 3.—To 500 ml of 0.01 *N* NaOH at 5° was added a solution of 0.376 g (1 mmol) of **3** in 5 ml of dioxane. After stirring for 0.5 hr at 5°, the solution was acidified to pH ~6 by the addition of 1 *N* HCl. A precipitate of phthalimide formed [0.101 g (69%), mp 225–231° (lit.[10] mp 238°)]. Tlc [silica gel, C_6H_6–Et_2O (5:2)] showed a major component having the same mobility as phthalimide and two minor components of lower mobility.

Hydrolysis of 4.—To a solution of 0.117 g (0.331 mmol) of **4** in a few drops of methanol was added 3 ml of 1 *N* NaOH previously cooled to 5°. After stirring at this temperature for 0.5 hr, the milky solution was acidified to pH ~6 by the addition of 1 *N* HCl. The resulting precipitate was filtered, washed with water, dried, and washed well with ether. Evaporation of the ether washings gave 0.011 g (27%) of benzyl disulfide, mp 65–67° (lit.[10] mp 69°). Tlc showed the ether-insoluble residue to be a mixture of at least four components.

Registry No.—**3**, 31892-91-8; **4**, 31862-24-5; **5**, 31862-25-6; **6**, 31892-92-9.

Acknowledgment.—We thank the Defense Research Board of Canada (Grant No. 9530-97) for financial support of this work.

(10) Handbook of Chemistry and Physics, 47th ed, Chemical Rubber Publishing Co., Cleveland, Ohio.

(11) Two small impurities revealed by tlc in the precursor thiol were also discovered in the product.

Pilloin, a New Flavone from *Ovidia Pillo-Pillo*

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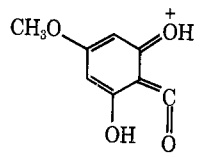
In connection with a general phytochemical investigation of the native vegetation of southern Chile, we report here the structure determination of a new flavone, pilloin ($C_{17}H_{14}O_6$, mp 236.5–237.5°), which was isolated from *Ovidia pillo-pillo* Meisner (formerly designated as *Dafne pillo-pillo* Gay), family *Thymelaeaceae*.

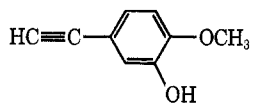
The nmr spectra of pilloin in pyridine-d_5 and its diacetyl and diethyl derivatives in $CDCl_3$ established that the natural product was a dimethyl ether of luteolin, and the mass spectrum of pilloin showed peaks at *m/e* 167 and 148 for fragments A and B, respectively,[1]

(1) H. Budzikiewicz, C. Djerassi, and D. H. Williams in "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964, p 262.

indicating that each aromatic ring contained one methoxyl group.



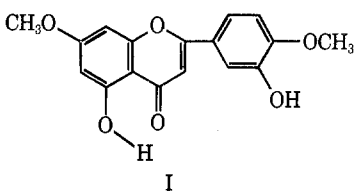
A



B

These spectral findings were supported by converting pilloin to both luteolin and luteolin tetramethyl ether.

Pilloin was shown to be different by direct comparison (ir, tlc, melting point, and mixture melting point) with velutin, luteolin 3′,7-dimethyl ether,[2] and, since the ultraviolet spectral curve with $AlCl_3$ (a bathochronic shift of 24 mμ of band I)[3] and ir (band at 3300 cm^{-1} for a hydrogen-bonded C-5 hydroxyl group) data established the presence of a C-5 hydroxyl group, pilloin must be the previously undescribed luteolin 4′-7-dimethyl ether (I). The ultraviolet spectrum in sodium acetate–ethanol confirmed that the 4′ position was blocked.[3]



I

Experimental Section[4]

Pilloin (3′,5-Dihydroxy-5′,7-dimethoxyflavone).—Leaves and branches of *Ovidia pillo-pillo* were collected in December 1968, in Los Ulmos, about 10 km south of Valdivia, Chile. Dried and ground material (2 kg) was extracted three times with 6 l. of ethanol at 50° for 12 hr. The ethanolic extract was concentrated under vacuum to give a syrup, which was poured into water (2 l.). The precipitate was discarded and the aqueous solution was then extracted with chloroform. On concentration a dark yellow precipitate was obtained, which was recrystallized from a methanol–chloroform mixture (2:1); with a yield of 0.2 g of pilloin: mp 235.5–236.5°; uv max 250, 270, and 330 mμ (log ε 4.13, 4.15, and 4.21); ir (KBr) 3300 (OH), 1660 (C=O), 1605, 1506, and 1455 (C=C), 813 cm^{-1} (two adjacent free hydrogen atoms); nmr (pyridine-d_5) 3.77 (s, OCH_3), 3.81 (s, OCH_3), 4.94 (s, 3′-OH), 6.61 (s, 2, 6 H and 8 H), 7.00 (s, 3 H), 7.08 (d, J = 8 Hz, 5′ H), 7.59 (q, J = 8, 2 Hz, 6′ H), and 7.89 (d, J = 2 Hz, 2′ H); mass spectrum 314 (parent), 285 (M − 29), 271 (M − 43), 167 ($C_8H_7O_4$), 148 ($C_9H_8O_2$), 138 ($C_7H_6O_3$), 133 ($C_8H_5O_2$), and 123 ($C_7H_7O_2$).

Anal. Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49. Found: C, 64.60; H, 4.76.

3′,5-Diacetoxy-4′,7-dimethoxyflavone.—Treatment of pilloin with acetic anhydride–pyridine formed the diacetate: uv max 232, 260, and 321 mμ (log ε 4.37, 4.17, and 4.46); nmr ($CDCl_3$) 2.35 (s, $OOCCH_3$), 2.42 (s, $OOCH_3$), 3.78 (s, $2OCH_3$), 6.47 (s, 3 H), 6.58 and 6.83 (each d, J = 2 Hz, 6 H and 8 H), 7.02 (d, J = 8.5 Hz, 5′ H), 7.54 (d, J = 2 Hz, 2′ H), 7.69 (q, J = 8.5, 2 Hz, 6′ H).

3′,5-Diethoxy-4′,7-dimethoxyflavone.—Ethylation of pilloin with diethyl sulfate–potassium carbonate gave the diethoxy derivative: mol wt 370 (mass spectrum); nmr ($CDCl_3$) 1.53 (2 t, 6, CH_2CH_3), 4.16 (2 q, 4, CH_2CH_3), 3.88 and 3.93 (each s, OCH_3), 6.33 and 6.51 (each d, J = 2 Hz, 6 H and 8 H), 6.52 (s, 3 H), 6.93 (d, J = 8 Hz, 5′ H), 7.30 (d, J = 2 Hz, 2′ H), 7.46 (q, J = 8, 2 Hz, 6′ H).

3′,4′,5,7-Tetramethoxyflavone.—Methylation of pilloin with dimethyl sulfate–potassium carbonate formed the tetramethoxy derivative, which was crystallized from benzene: mp 190–191° (lit.[5] mp 192–193°); mass spectrum 342 (parent), 341 (M − 1), 313 (M − 29), 312 (M − 30), 162 ($C_{10}H_{10}O_2$), 152 ($C_8H_8O_3$), 147 ($C_9H_7O_2$), 137 ($C_8H_9O_2$).

3′,4′,5,7-Tetrahydroxyflavone, Luteolin.—Demethylation of pilloin with hydrogen iodine gave luteolin. The ultraviolet spectra in ethanol was identical with an authentic sample of luteolin.[6] The ultraviolet shifts with sodium acetate–ethanol were almost identical with those reported for luteolin.[7]

Registry No.—1, 32174-62-2; 1 deacetate, 32174-63-3; 1 diethyl ether, 32174-64-4; 1 tetramethyl ether, 855-97-0.

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(2) K. C. Das, W. J. Farmer, and B. Weinstein, *J. Org. Chem.*, **35**, 3989 (1970). The author thanks Professor B. Weinstein, University of Washington, for a sample of velutin.

(3) L. Jurd in "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., Macmillan, New York, N. Y., 1962, p 107.

(4) Melting points are uncorrected. Mass spectrum, nuclear magnetic resonance (internal tetramethylsilane, 100 MHz) and mycroanalysis were generously provided by the University of Zurich, through Dr. Jorge Naranjo, whose cooperation I gratefully thank. Thin layer chromatography employed silica gel G as a support, chloroform as the developer, and iodine for detection.

(5) J. Grinpenberg in "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., Macmillan, New York, N. Y., 1962, p 406.

(6) The author thanks Professor C. Galeffi, Instituto Chimico dell'Universitá, Torino, and Professor S. Tira, Instituto Superiore di Sanitá, Roma, for samples of luteolin.

(7) B. Valdes, *Phytochemistry*, **9**, 1253 (1970).

A Directing Effect of Oxygen in Perhydrophthalans

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Pasto's recent evaluation of the directive effects caused by a 3-alkyl group in substituted cyclohexenes[2] prompts us to report our work related to this problem. As part of an investigation directed toward the synthesis of guaianolide sesquiterpenes, we chose as one of our models 7-methyl-*cis*-3a,4,7,7a-tetrahydrophthalan-5-one (2), presumably to be prepared by a sequence as delineated in eq 1.[3] It became apparent during the early phases of our research, however, that we might be able to observe some directive effects caused by the phthalan oxygen during hydration of **1**, and we accordingly attempted an analysis of regiospecific[7] directive effects. Of the several methods available for hydration we chose to investigate hydroboration with diborane and disiamylborane and oxymercuration. In all cases studied, the alcohols resulting from the hy-

(1) NDEA Predoctoral Fellow, 1968–1971.

(2) D. J. Pasto and J. A. Gontarz, *J. Amer. Chem. Soc.*, **92**, 7480 (1970).

(3) The ease of preparation of phthalan derivatives has resulted in their occasional use as models for the corresponding carbocyclic systems. The various oxygen-containing models have been useful for mechanism studies[4] and synthetic work.[5] The question of whether there are electronic and directive effects associated with the heteroatom has been raised.[6]

(4) E. L. Eliel and C. Pillar, *J. Amer. Chem. Soc.*, **77**, 3600 (1955).

(5) A. P. Krapcho and B. P. Mundy, *J. Org. Chem.*, **32**, 2041 (1967).

(6) B. Rickborn and S. Y. Lwo, *ibid.*, **30**, 2212 (1965).

(7) A. Hassner, *Accounts Chem. Res.*, **4**, 9 (1971).