dicative of the pyrophosphate group.[19] When the purified material was heated to its melting point, decomposition occurred, and dimethylamine could be detected by its characteristic odor: ir (film) 2.94 (NH), 7.83 (P=O), and 10.32 μ (POP).

Anal. Calcd for $C_4H_{18}N_2O_7P_2$: C, 18.0; H, 6.7; N, 10.5; P, 23.1. Found: C, 18.3; H, 6.5; N, 10.5; P, 23.4.

Registry No.—HMPT, 680-31-9; *trans*-2-phenylcyclohexanol, 2362-61-0; *trans*-1(a)-decalol, 31729-83-6; bis(dimethylammonium) dihydrogen pyrophosphate, 31729-84-7.

Ackowledgment.—The authors express their appreciation to the Research Foundation of California State College at Hayward for financial support.

(19) W. M. Latimer and J. H. Hildebrand, "Reference Book of Inorganic Chemistry," 3rd ed, Macmillan, New York, N. Y., 1951, p 232.

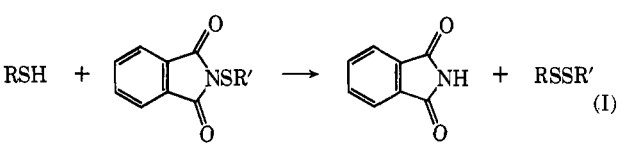
The Synthesis of Some New Cysteine-Containing Unsymmetrical Disulfides[1]

DAVID N. HARPP* AND THOMAS G. BACK

Department of Chemistry, McGill University, Montreal, Canada

Received May 20, 1971

It was recently found[2] that a convenient route for the synthesis of dialkyl and aralkyl unsymmetrical disulfides is the thiolysis of the corresponding thiophthalimide as shown in eq I. Excellent yields, stable precursors, and minimal disulfide interchange are among the advantages offered by this method. Some of the disulfides prepared in this manner were the simple peptides, *S*-benzylthioglutathione and *S*-benzylthio-L-cysteine hydrochloride (R′ = benzyl in eq I).

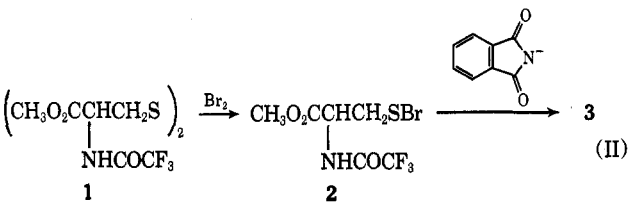


(I)

We now wish to report the synthesis of a cysteine-containing thiophthalimide, which has provided us with an excellent synthetic route *via* eq I to some new unsymmetrical disulfides, in two of which both R and R′ are cysteine or glutathione residues.

A 65% yield of *N*-trifluoroacetyl-*S*-phthalimido-L-cysteine methyl ester (**3**) (Table I) was obtained (eq II) by first brominating[3] disulfide[4] **1** at 0°, and then treating the resulting sulfenyl bromide **2** with the phthalimide anion.

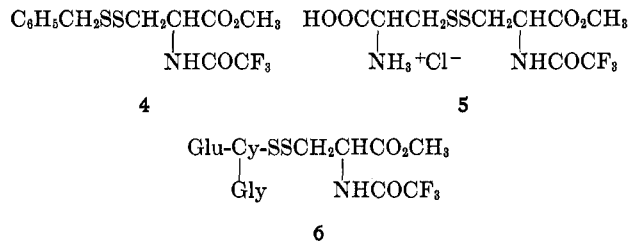
Although **2** was used directly without isolation, evidence for its formation derives from nmr data. The methylene absorption of **2** in trifluoroacetic acid solution is shifted 0.3 ppm downfield relative to that of **1**. This appears reasonable, since the methylene absorption of the chlorine analog of **2** is found[5] 0.5 ppm downfield from that of **1**.



(II)

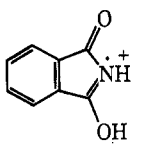
1 2

Thiolysis of **3** with benzyl mercaptan, cysteine hydrochloride monohydrate, and glutathione, according to eq I, gave excellent yields (92–99%) of the corresponding disulfides **4**, **5**, and **6**, respectively. Absence of the corresponding symmetrical disulfides in the products



4 5 6

was established by tlc, except in the case of **6** where traces were found. The structures of compounds **3–6** were consistent with infrared, nmr, mass spectral, and elemental analyses. The mass spectrum of **3** shows an intense peak at *m/e* 148, likely due to formation of fragment a.



a

Major peaks reported[6] in the mass spectra of other thiophthalimides (at *m/e* 147, 130, 104, and 76) were also observed.

Disulfides **4–6** showed fragmentation similar to **1** as previously reported.[4] Cleavage of both the disulfide bond and the C–S bond on the side of the blocked cysteine residue was evident from intense peaks at *m/e* 230 and 198, respectively.

Attempts to selectively remove the trifluoroacetyl and methyl ester protective groups by mild alkaline hydrolysis of thiophthalimide **3** and disulfide **4** were unsuccessful, as both the S–N[7a] and S–S[7b] linkages proved too labile to withstand even the mild basic conditions[8] required to remove the trifluoroacetyl group. Treatment of **3** with 0.01 *N* NaOH at 5° for 0.5 hr gave 69% of phthalimide.[9] Reaction of **4** with 1 *N* NaOH under similar conditions gave 27% of benzyl disulfide.[9]

Thus it is clear that thiolysis of a cysteine thiophthalimide with an alkyl thiol, cysteine, or glutathione, provides a rapid, clean, and almost quantitative syn-

(1) Organic Sulfur Chemistry. XII. For part XI, see D. N. Harpp and D. K. Ash, *Int. J. Sulfur Chem.*, in press.

(2) (a) K. S. Boustany and A. B. Sullivan, *Tetrahedron Lett.*, 3547 (1970); (b) D. N. Harpp, D. K. Ash, T. G. Back, J. G. Gleason, B. A. Orwig, W. F. Van Horn, and J. P. Snyder, *ibid.*, 3551 (1970).

(3) The yield of sulfenyl bromide was considered to be quantitative; treatment of the corresponding sulfenyl chloride with the phthalimide anion resulted in the formation of significant amounts of phthalimide, thus indicating proton abstraction. No other identifiable products resulted.

(4) The yield of disulfide was 95%: D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **36**, 73 (1971).

(5) P. Mathiaparanam, Ph.D. Thesis, McGill University, 1971.

(6) B. A. Orwig, M.Sc. Thesis, McGill University, 1971.

(7) (a) J. E. Kerwood and M. Behforouz, *J. Org. Chem.*, **34**, 51 (1969); (b) A. Parker, and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

(8) It has been reported that the trifluoroacylamide bond is labile at pH greater than 10: E. Schallenberg and M. Calvin, *J. Amer. Chem. Soc.*, **77**, 2779 (1955).

(9) The remaining reaction mixture was not further investigated.

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*

J. NÚÑEZ-ALARCÓN

Instituto de Química, Universidad Austral de Chile, Valdivia, Chile

Received April 26, 1971

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.