10% sodium hydroxide, and the filtrate reprecipitated with 50% acetic acid. The chloromercuri compound was refluxed with iodine in chloroform and worked up as described in the preparation of I to yield 9 g. of product, m.p. 88°, and 5 g., m.p. 173°. These solids are identical in melting points and infrared spectra with those obtained in a similar synthesis using potassium iodide in place of sodium chloride. The proof of their structure will be reported elsewhere.

*meso-1,4-Diiodo-2,3-diethoxybutane* (VII). Butadiene was bubbled through a mixture of 32 g. (0.1 mole) of mercuric acetate in 150 cc. of absolute ethanol to form a precipitate. Aqueous sodium chloride was added to the suspension, and the resulting water-insoluble precipitate was filtered, dissolved in 10% sodium hydroxide, and reprecipitated with 50% acetic acid. The solid was treated as described in the preparation of I and 6 g. of material, m.p. 45–47°, was obtained. This was identical with VII prepared by the method of Johnson and co-workers.[7]

*Treatment of diiodides with mercuric chloride. a. Conversion of* I *to* II. A 0.7-g. sample of I (0.002 mole) was refluxed with 0.3 g. of mercuric chloride in 35 cc. of chloroform for 119 hr. The yellow mercuric salt formed was filtered, and the filtrate evaporated to leave a solid, m.p. 108°, whose infrared spectrum matched that of II.

b. Preparations of other chloroiodides are compiled in Table I.

c. When *trans*-2,3-bis(iodomethyl)-*p*-dioxane and *cis*-2,6-bis(iodomethyl)-*p*-dioxane were treated with 1 equivalent of mercuric chloride as above, they were recovered unchanged almost quantitatively after 5 days. When II and IX were treated with 1 equivalent of mercuric chloride as above, they were recovered unchanged. When III was treated with 2 equivalents of mercuric chloride, the only material found was IX.

*Preliminary vapor phase chromat graphy studies an α,ω-alkyldiiodides.* The treatment of 1,4-diiodobutane with mercuric chloride is representative of the experiments performed on all the alkyldiiodides. A mixture of 5 g. (0.016 mole) of 1,4-diiodobutane and 4.4 g. (0.016 mole) mercuric chloride was refluxed in 21 cc. of chloroform for 4 days, and 0.5-cc. samples were withdrawn at intervals. Excess solvent was allowed to evaporate. At the end of the 4 days, the samples were injected into an Aerograph vapor phase chromatograph containing a 10-ft. column of 8% 550 Silicon Oil on firebrick and maintained at 200°. The percentages of components present in each sample were calculated from the ratio of the areas of the peaks recorded. Peak areas were obtained as the product of peak height times width at half-height. A graph of time *vs.* per cent composition was plotted to indicate the relative rates of formation of monochloro- and dichloro- derivatives.

EVANSTON, ILL.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, PHARMACEUTICAL FACULTY, UNIVERSITY OF ZAGREB AND RESEARCH INSTITUTE "PLIVA," PHARMACEUTICAL AND CHEMICAL WORKS]

# Fragmentation of α-Phthalimido-β-methylmercaptopropiophenone with Aluminum Chloride[1]

DRAGUTIN FLEŠ,[2] MIROSLAV DADIĆ,[3] ANICA MARKOVAC-PRPIC, AND MELITA FLES

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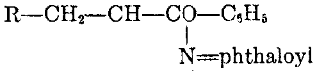
Under the normal conditions of Friedel-Crafts reaction with benzene, the title compound yielded various products depending on the amount of aluminum chloride. With one mole of aluminum chloride the unchanged acid chloride was isolated, while with two moles of catalyst, α-phthalimido-β-methylmercaptopropiophenone was obtained. With three moles of aluminum chloride, *S*-methyl-*N*-phthaloylcysteinyl chloride or α-phthalimido-β-methylmercaptopropiophenone underwent a fragmentation reaction, yielding phthalimidoacetophenone and diphenylmethane.

As shown by experiments in these laboratories α-phthalimidopropionyl chloride and its β-methoxy and β-ethoxy derivatives react with benzene in the presence of aluminum chloride to yield the normal products of Friedel-Crafts reaction.[4] The yield of propiophenone derivatives, however, largely depended on the character of the β-substituents (Table I).

When *S*-benzyl-*N*-phthaloyl-L-cysteinyl chloride was subjected to the same reaction, L-α-phthalimido-β-propiothiolactone (I) was obtained with two moles of aluminum chloride, while a polythio ester (II) was isolated when the reaction had been performed with one mole of catalyst.[5]

TABLE I



$$\mathrm{R{-}CH_2{-}\underset{\substack{|\\ N{=}phthaloyl}}{CH}{-}CO{-}C_6H_5}$$

| R | Yield, % |
|---|---|
| $OCH_3$ | 63 |
| $OC_2H_5$ | 25 |
| H | 90 |
| $SCH_3$ | 51 |

Continuing the studies of the course of Friedel-Crafts reaction with substituted propionyl chlorides, the reaction of *S*-methyl-*N*-phthaloylcysteinyl chloride with aluminum chloride in benzene was

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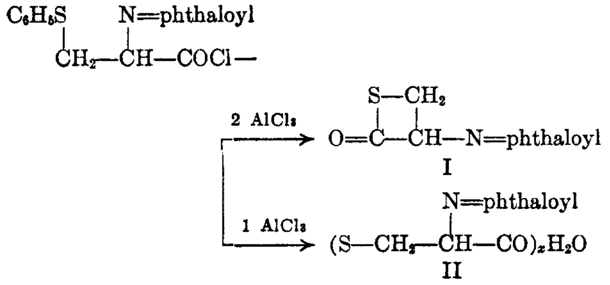
[1] Presented before 1st Yugoslav Congress of Pure and Applied Chemistry, Zagreb, June 1960.

[2] Present address: Organsko Kemijska Industrija, Boškovićeva 33, Zagreb.

[3] Taken from the thesis submitted by M.D. in partial fulfillment of the requirement for the degree of Doctor of Chemistry at the University of Zagreb.

[4] D. Fleš, B. Balenović, R. Marušić, and N. Manger, *Arhiv. kem.*, **27**, 1 (1955); D. Fleš and B. Balenović, *Arhiv. kem.*, **27**, 149 (1955); D. Fleš and A. Markovac-Prpić, *Croat. Chem. Acta*, **29**, 183 (1957).

[5] D. Fleš, A. Markovac-Prpić, and V. Tomašić, *J. Am. Chem. Soc.*, **80**, 4654 (1958).

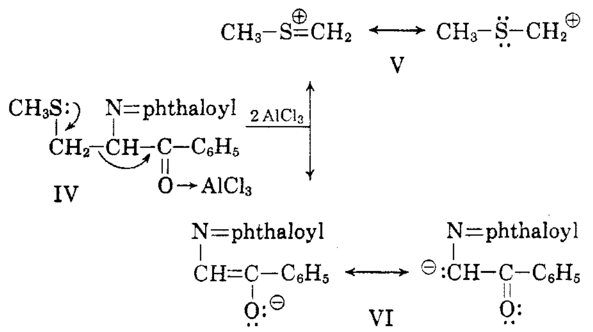


examined. It was found during these studies that under the normal conditions of Friedel-Crafts reaction, no demethylation occurred, but depending on the amount of catalyst, various products were isolated.

With one mole of aluminum chloride in benzene or in carbon disulfide as co-solvent, the unchanged *S*-methyl-*N*-phthaloylcysteinyl chloride, which was subsequently converted to ethyl ester, was isolated in practically quantitative yield. When two moles of catalyst was used, the normal product of Friedel-Crafts reaction, α-phthalimido-β-methylmercaptopropiophenone, was isolated in 51% yield. The reaction was studied further with three moles of aluminum chloride and, unexpectedly, it was found that a Cα-Cβ cleavage occurred, and phthalimidoacetophenone was isolated as the main reaction product. Another product hereby identified was diphenylmethane. Phthalimidoacetophenone was also obtained when α-phthalimido-β-methylmercaptopropiophenone was treated with three moles of aluminum chloride, which indicated that the propiophenone derivative is an intermediate in the reaction with three moles.

The mechanism of these reactions can best be explained as follows: One mole of aluminum chloride forms initially with the acid chloride the acyl halide-aluminum halide addition complex, which combines with the sulfur of other molecules, yielding a complex insoluble in benzene. The second molecule of aluminum chloride forms the complex with *S*-methyl-*N*-phthaloylcysteinyl chloride which reacts normally, yielding the expected product of the Friedel-Crafts acylation reaction.

The structure of the complex molecule IV shows that it can easily undergo a heterolytic cleavage, according to C. A. Grob.[6] All conditions for a fragmentation reaction are fulfilled in the molecule IV, and the third molecule of the catalyst causes an ionization of the molecule with the formation of unsaturated fragments V and VI. The fragment molecules V and VI are stabilized by activated benzene molecules, giving rise to phthalimidoacetophenone and benzyl methyl sulfide. Benzyl methyl sulfide has not been isolated from the system since it undoubtedly undergoes a fast debenzylation rection.[7] The benzyl carbonium ion formed through the debenzylation reaction easily recombines with activated benzene, yielding diphenylmethane, as proved by vapor phase chromatography.



The fragmentation reaction described in this paper can be considered to be a sulfur-for-oxygen-analog of the reverse aldol reaction, and is the first reaction of this type involving a sulfur-containing compound.

### EXPERIMENTAL[8]

*S-Methyl-*DL*-cysteine.* *S*-Benzyl-DL-cysteine[9] (12 g., 0.057 mole) was reduced with 2.6 g. (0.113 mole) of sodium in liquid ammonia and the resulting cysteine methylated with 8.9 g. (0.064 mole) of methyl iodide, following essentially the procedure for the preparation of optically active product[10]; m.p. 225°; reported m.p. 205–207°[11] and 240°.[12]

*Anal.* Calcd. for $C_4H_9NO_2S$: C, 35.55; H, 6.71. Found: C, 35.50; H, 6.40.

*S-Methyl-N-phthaloylcysteine.* A. *Via phthalic anhydride method.* A finely powdered mixture of 3 g. (0.022 mole) of *S*-methylcysteine and 3.5 g. (0.027 mole) of phthalic anhydride was placed in a round bottomed flask and heated in an oil bath with a thermometer immersed in the reaction mixture. A vigorous evolution of water started at 140° and the reaction mixture melted. Heating was continued for 1 hr. at the temperature of 140–150°. In some preparations the reaction mixture solidified at that temperature. After cooling, the crude phthaloyl derivative was dissolved in 30 ml. of methanol and crystallized by addition of 50 ml. of water. The crude product (4.1 g.) was dissolved in 20 ml. of methanol, treated with charcoal, and precipitated with water; yield, 3.1 g. (52.7%), m.p. 185–186°.

*Anal.* Calcd. for $C_{12}H_{11}NO_4S$: C, 54.32; H, 4.18; N, 5.28. Found: C, 54.34; H, 4.08; N, 5.30.

B. *Via N-carbethoxyphthalimide.* The solid *N*-carbethoxyphthalimide[13] (1 g., 0.046 mole) was added at once to a solution of 0.54 g. (0.004 mole) of *S*-methylcysteine and 0.424 g. (0.004 mole) of sodium carbonate in 6 ml. of water. The reaction mixture was vigorously stirred for 10 min., filtered from undissolved *N*-carbethoxyphthalimide, acidified to *p*H 1–2 with concentrated hydrochloric acid, and the oily precipitate was dissolved by boiling the reaction mixture for a few minutes. Crystalline product which separated on cooling was removed by suction filtration and recrystallized from methanol-water, yielding 0.45 g. (42%) of *S*-methyl-*N*-phthaloylcysteine; m.p. and mixed m.p. 185–186°.

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(6) C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1954); C. A. Grob, *Experientia*, **13**, 126 (1957).

(7) D. P. Harnish and D. S. Turbell, *J. Am. Chem. Soc.*, **70**, 4123 (1948).

(8) The melting points are uncorrected. All compounds described in this paper are racemic.

(9) V. du Vigneaud and J. L. Wood, *J. Biol. Chem.*, **130**, 110 (1939).

(10) V. du Vigneaud, H. S. Loring, and H. A. Craft, *J. Biol. Chem.*, **105**, 481 (1934).

(11) N. Izumiya, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **72**, 1050 (1951).

(12) G. Nadeau and R. Gaudry, *Can. J. Research*, **27B**, 421 (1949).

(13) G. H. Nefkens, G. J. Tessar, and R. J. F. Nivard, *Rec. Trav. Chim.*, **71**, 688 (1960).

*Anal.* Found: N, 5.34.

*S-Methyl-N-phthaloylcysteinyl chloride. S*-Methyl-*N*-phthaloylcysteine (5 g., 0.0184 mole) was heated for 1 hr. at 70° with 16 ml. of thionyl chloride and 16 ml. of benzene. The excess of thionyl chloride and benzene was removed *in vacuo,* the residue repeatedly treated with benzene and dried over potassium hydroxide in a vacuum desiccator. This product was directly used in the next conversion. A sample was purified for analysis by crystallization from a mixture of benzene and petroleum ether (b.p. 40–60°) (1:3), m.p. 90–91°.

*Anal.* Calcd. for $C_{12}H_{10}ClNO_3S$: N, 4.93. Found: N, 5.18.

*Reaction of S-methyl-N-phthaloylcysteinyl chloride with two moles of aluminum chloride.* To a mixture of 5.7 g. (0.043 mole) of aluminum chloride and 50 ml. of carbon disulfide was added in one portion a solution of 5.4 g. (0.019 mole) of *S*-methyl-*N*-phthaloylcysteinyl chloride in 85 ml. of benzene. The reaction mixture was stirred vigorously for 3.5 hr. at a temperature of 55–60°, cooled, and hydrolyzed with 50 g. of ice and 10 ml. of concd. hydrochloric acid. The aqueous layer was separated and extracted with two 20-ml. portions of benzene, the combined benzene layers were washed with water until neutral to litmus, dried, and evaporated *in vacuo.* The semicrystalline residue was treated with 2 ml. of ethanol, transferred to a small beaker, triturated with 5 ml. of ethanol and the crystalline product, *α-phthalimido-β-methylmercaptopropiophenone,* removed by suction filtration; yield, 2.9 g. (51%), m.p. 126–128°. A sample for analysis was crystallized twice from ethanol; m.p. 132–133°.

*Anal.* Calcd. for $C_{18}H_{15}NO_3S$: C, 66.45; H, 4.65. Found: C, 66.16; H, 4.47.

The 2,4-dinitrophenylhydrazone was prepared in quantitative yield in an alcoholic solution. The analytical sample was crystallized from a mixture of ethanol and chloroform, m.p. 216–217°.

*Anal.* Calcd. for $C_{24}H_{18}N_5O_6S$: N, 13.89. Found: N, 13.94.

*Reaction of S-methyl-N-phthaloylcysteinyl chloride with one mole of aluminum chloride.* To a mixture of 10 ml. of carbon disulfide and 0.65 g. (0.0048 mole) of aluminum chloride was added in one portion a solution of 1.15 g. (0.0041 mole) of *S*-methyl-*N*-phthaloylcysteinyl chloride in 15 ml. of benzene. The reaction mixture was vigorously stirred and treated in the same manner as described in the reaction with two moles of aluminum chloride. The product obtained upon hydrolysis and evaporation of benzene was dissolved in ethanol and left over night at room temperature. Ethanol was evaporated *in vacuo* and the oily residue distilled at 130–140° at a pressure of 0.1 mm., yielding colorless oil which was proved to be identical with the ethyl ester of *S*-methyl-*N*-phthaloylcysteine, as shown by identical infrared spectra.

*Anal.* Calcd. for $C_{14}H_{15}NO_4S$: C, 57.33; H, 5.16. Found: C, 57.11; H, 5.09.

*Reaction of S-methyl-N-phthaloylcysteinyl chloride with three moles of aluminum chloride.* The reaction was performed with 2.9 g. (0.01 mole) of *S*-methyl-*N*-phthaloylcysteinyl chloride and 4 g. (0.03 mole) of aluminum chloride in the same way as previously described, and 1.0 g. (37%) of phthalimidoacetophenone was isolated; m.p. 167–168°. In admixture with an authentic specimen of phthalimidoacetophenone,[14] the melting point was undepressed.

*Anal.* Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.14; H, 4.03; N, 5.02.

The 2,4-dinitrophenylhydrazone was prepared in ethanol and crystallized from a mixture of ethanol and chloroform, m.p. and mixed m.p., 234–235°.

*Anal.* Calcd. for $C_{22}H_{15}N_5O_6$: C, 59.32; H, 3.39. Found: C, 59.70; H, 3.59.

*Phthalimidoacetophenone oxime.* A mixture of 0.267 g. (0.001 mole) of phthalimidoacetophenone and 0.14 g. (0.002 mole) of hydroxylamine hydrochloride was dissolved in 2 ml. of pyridine and left at room temperature for 2 days. The pyridine was evaporated *in vacuo,* the residue treated with 5 ml. of water, and the crystalline product (0.25 g.) recrystallized three times from ethanol, m.p. 181–183°.

*Anal.* Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32. Found: C, 68.83; H, 4.25.

The ethanolic mother liquor from which the phthalimidoacetophenone was obtained, gave on evaporation 2 g. of oily residue, which was extracted with three 25-ml. portions of petroleum ether (b.p. 40–60°), and after the solvent was evaporated, 0.5 g. of colorless oil resulted. The oily extract was distilled at 60–65° and 0.1 mm., and a sample submitted to vapor phase chromatography.[15] Diphenylmethane and an unidentified sulfur containing compound were detected.

*Reaction of α-phthalimido-β-methylmercaptopropiophenone with three moles of aluminum chloride.* α-Phthalimido-β-methylmercaptopropiophenone (0.325 g., 0.001 mole) was treated with 0.4 g. (0.003 mole) of aluminum chloride in the same manner as previously described in the reaction of *S*-methyl-*N*-phthaloylcysteinyl chloride. Phthalimidoacetophenone was isolated with 75.5% yield (0.2 g.); m.p. and mixed m.p. 167–168°.

*Anal.* Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18. Found: C, 72.25; H, 3.84.

Diphenylmethane was proved in the same way as previously described.

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ZAGREB, YUGOSLAVIA

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[14] S. Gabriel, *Ber.,* **40,** 2649 (1907).

[15] "Aerograph" A-90 Wilkins instrument with a silicon oil supported by fire brick column was used. The gas carrier was hydrogen.