1705 cm.$^{-1}$ (s); ultraviolet, λ_{max} 265 mμ (ε 400); λ_{min} 240 mμ (ε 200).

Anal. Calcd. for $C_{15}H_{18}OCl_2$: C, 63.17; H, 6.35; Cl, 24.87. Found: C, 63.50; H, 6.56; Cl, 24.4.

Its 2,4-dinitrophenylhydrazone crystallized from ethanol–ethyl acetate as yellow plates, m.p. 169–170°.

Anal. Calcd. for $C_{21}H_{22}O_4N_4Cl_2$: C, 54.20; H, 4.77; N, 12.04. Found: C, 54.06; H, 4.72; N, 12.2.

The ketone VIII was isolated sometimes as prisms melting at 93–94°. The mixed m.p. of the two crystalline modifications was 92–94°. Their infrared spectra were identical, and their 2,4-dinitrophenylhydrazones had the same m.p. (169–170°) and showed no depression on admixture.

A mixture of 200 mg. of ketol VII, 100 mg. of 5% palladium-on-charcoal catalyst and 1.25 ml. of concentrated sulfuric acid in 25 ml. of ethyl acetate was hydrogenated at atmospheric pressure. After 24 hr. a two-mole hydrogen uptake was attained. The mixture was filtered, washed with sodium bicarbonate solution and water and evaporated. Recrystallization of the residue in petroleum ether yielded white crystals, m.p. 80–81°, whose lack of mixed m.p. depression and identity of infrared spectrum with the ketone VIII proved its identity with the latter.

4a-Methyl-4a,9,10,10a-tetrahydro-2(1H)-phenanthrone (IX).—A 200-ml. ether solution of 28.6 mmoles of sodium triphenylmethyl was added under a nitrogen atmosphere to 1.00 g. (3.5 mmoles) of ketone VIII. The solution was left standing at room temperature for 3 days with occasional shaking. After a final 5 hr. reflux on the steam-bath, the deep red mixture was cooled, hydrolyzed with water containing a little acetic acid and extracted 5 times with ether. The organic extract was washed with sodium bicarbonate solution and water, dried over magnesium sulfate and evaporated. The residue was extracted five times with hot petroleum ether and the cooled extract placed on a Celite–silicic acid chromatography column. The 19:1 petroleum ether–ether eluate gave 230 mg. of solid, m.p. 98–100°. Rechromatography under identical conditions of the noncrystalline fractions, whose infrared spectra made them appear to contain more unsaturated ketone, led to an additional 90 mg. of product. Three recrystallizations from petroleum ether yielded white crystals, m.p. 103–104°; spectra: infrared, C=O 1670 cm.$^{-1}$(s); ultraviolet, λ_{max} 228 mμ (ε 14,000).

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.96, 85.21; H, 7.38, 7.61.

Its 2,4-dinitrophenylhydrazone crystallized as red platelets from ethanol–ethyl acetate; m.p. 205–206°.

Anal. Calcd. for $C_{21}H_{20}O_4N_4$: C, 64.27; H, 5.14; N, 14.28. Found: C, 63.94; H, 5.20; N, 13.8.

The chromatographic fractions immediately preceding the hydrophenanthrone contained considerable amounts of unreacted acetonyl compound VIII, as indicated by their infrared spectra.

***trans*-4a-Methyl-3,4,4a,9,10,10a-hexahydro-2(1H)-phenanthrone (X).**—A mixture of 200 mg. of tricyclic ketone IX and 50 mg. of 5% palladium-on-charcoal catalyst in 20 ml. of ethanol was hydrogenated at one atmosphere. Hydrogen absorption ceased after 15 minutes and an uptake of one mole. The mixture was filtered, evaporated and the residue crystallized in petroleum ether, yielding white plates, m.p. 107–108°. Its m.p., mixed m.p. and infrared spectrum and those of its semicarbazone and *p*-nitrophenylhydrazone showed it to be the previously reported[6] *trans*-hydrophenanthrone X.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Isomerism of Dithiolphthalates

BY JOHN C. SHEEHAN AND GERALD F. HOLLAND[1]

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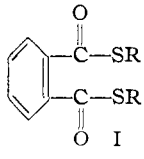
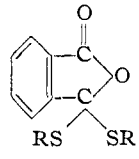
Both of the possible isomeric structures (symmetrical and unsymmetrical) for diphenyl dithiolphthalate and for di-(*p*-nitrophenyl) dithiolphthalate have been obtained in pure form and structures assigned on the basis of infrared spectra. *sym*-Diphenyl dithiolphthalate was prepared in 94% yield by interaction of *sym*-phthaloyl chloride, thiophenol and sodium methoxide in methanol solution. By treatment of a mixture of phthalic anhydride and thiophenol with phosphorus pentoxide, there was produced a mixture of isomers from which the pure *unsym*-diphenyl dithiolphthalate was isolated. *sym*-Di-(*p*-nitrophenyl) dithiolphthalate, synthesized from *sym*-phthaloyl chloride and *p*-nitrothiophenol in the presence of pyridine, was isomerized to the unsymmetrical form in basic solution. Treatment of glycine and of ethyl glycinate with *sym*-di-(*p*-nitrophenyl) dithiolphthalate at room temperature afforded phthaloylglycine and ethyl phthaloylglycinate (ethyl phthalimidoacetate), respectively.

Two isomeric structures may be written for dithiolphthalates: symmetrical isomer I and unsymmetrical isomer II.[2-4] Troeger and Hornung, after treating lead thiophenolate with phthaloyl chloride, obtained a compound, m.p. 84–85°, to which they assigned structure I in which R = C_6H_5. Two compounds[3] were isolated after heating a mixture of phthalic anhydride, thiophenol and phosphorus pentoxide, m.p. 84–85° and m.p. 101°.



I



II

It was stated, "neither of these could be hydrolyzed by boiling with aqueous alkali, which indicates that neither has the lactone structure adopted for one of them by Troeger and Hornung. These two compounds are isomeric and the difference between them is not clear." Similar results were observed by heating thiophenol and phthaloyl chloride in benzene.

Knapp,[4] by treatment of phthaloyl chloride and phenyl thiolacetate with aluminum chloride, obtained a compound, m.p. 101°, which was designated as the lactone structure II (R = C_6H_5). This assignment was based on the well-known conversion by aluminum chloride[5] of symmetrical phthaloyl chloride into unsymmetrical phthaloyl chloride, which could then react with phenyl thiolacetate to give unsymmetrical diphenyl dithiolphthalate. In the present investigation the procedure of Chakravarti and Saha[3] was repeated and two compounds

(1) This work was aided by a contract from the Office of Naval Research.

(2) J.Troeger and V. Hornung, *J. prakt. Chem.*, **66**, 345 (1902).

(3) G. C. Chakravarti and J. M. Saha, *J. Indian Chem. Soc.*, **4**, 141 (1927).

(4) W. Knapp, *Monatsh.*, **58**, 176 (1931).

(5) E. Ott, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 528.

were isolated. The product melting at 101° has a strong absorption band in the infrared at 1760 cm.$^{-1}$; this corresponds to the typical carbonyl stretching frequency of a γ-lactone.[6] This result confirms Knapp's assignment of structure II (R = C_6H_5) for isomer melting at 101°.

The second product melted at 80–88°, a wider range than reported. The infrared spectrum shows two strong carbonyl absorption-type bands at 1760 and 1670 cm.$^{-1}$; these are characteristic of the carbonyl stretching vibration of a γ-lactone and thiolester.[6] Thus the product of melting point 84–85° isolated by Troeger and Hornung and also by Chakravarti and Saha apparently is a mixture of isomers I and II (R = C_6H_5).

Symmetrical diphenyl dithiolphthalate was prepared in 94% yield by treating symmetrical phthaloyl chloride with a solution of thiophenol in methanol–sodium methoxide. Isomer I (R = C_6H_5) melted at 130–130.6° and its spectrum shows only a strong carbonyl-type band at 1670 cm.$^{-1}$ corresponding to a thiolester. The reaction between symmetrical phthaloyl chloride and thiophenol in the presence of triethylamine resulted only in a mixture of isomers as determined by infrared. Isomer I (R = C_6H_5) on treatment with benzylamine at 25° in dioxane solution gave a 75% yield of N,N′-dibenzylphthalamide.

Kenner[7] recently reported the high order of reactivity of the *p*-nitrophenyl thiolesters in peptide syntheses. The relative rates of reaction between alanine and the *p*-nitrophenyl thiolester, phenyl thiolester and the *p*-nitrophenyl ester of carbobenzyloxyglycine were 140:1:16. Symmetrical di-(*p*-nitrophenyl) dithiolphthalate (I, R = *p*-$C_6H_4NO_2$) was prepared in order to study the reactions of this diester with various amines and amino acids.

Reaction conditions similar to those employed in the synthesis of I (R = C_6H_5) gave only di-(*p*-nitrophenyl) disulfide. However by the slow addition of symmetrical phthaloyl chloride and pyridine to an acetone solution of *p*-nitrothiophenol,[8] a 74.5% yield of I, R = *p*-$C_6H_4NO_2$, was obtained. The infrared spectrum shows only the band at 1670 cm.$^{-1}$ characteristic of a thiolester and no band of the γ-lactone type was observed. A mixture of this dithiolester, triethylamine and tryptophan ethyl ester hydrochloride[9] resulted chiefly in the isomerization of I to II (R = *p*-$C_6H_4NO_2$).

Symmetrical di-(*p*-nitrophenyl) dithiolphthalate reacted with glycine ethyl ester[10] at 25° to yield 75% of ethyl phthalimidoacetate. Glycine and I (R = *p*-$C_6H_4NO_2$) on treatment in a sodium bicarbonate solution gave a 24% yield of phthaloylglycine and 40% yield of the unsymmetrical isomer II. These reactions constitute the first recorded synthesis of a phthaloyl derivative from an amino acid and an amino acid ester at room temperature. The isomerization of I to II, R = *p*-$C_6H_4NO_2$, was carried out by equilibrating I with triethylamine in methylene chloride solution at 25°.

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 159–161.

(7) J. A. Farrington, G. W. Kenner and J. M. Turner, *Chemistry & Industry*, **21**, 601 (1955).

(8) C. C. Price and G. W. Stacy, THIS JOURNAL, **68**, 499 (1946).

(9) C. P. Berg, W. C. Rose and C. S. Marvel, *J. Biol. Chem.*, **85**, 210 (1929–1930).

(10) E. Fischer, *Ber.*, **34**, 436 (1901).

Experimental[11]

The Reaction between Phthalic Anhydride, Thiophenol and Phosphorus Pentoxide.—The following procedure is a modification of that described by Chakravarti and Saha.[3] A well-stirred mixture of 6.0 g. (0.04 mole) of phthalic anhydride, 8.2 ml. (0.08 mole) of thiophenol and 3.0 g. of phosphorus pentoxide was heated in an oil-bath at 140° for 3 hours. The liquid was decanted and the solidified product was collected by filtration. The colorless solid was dissolved in 100 ml. of benzene and the solution extracted successively with three 100-ml. portions of 10% sodium bicarbonate solution followed by water. After drying, the benzene was removed by distillation under reduced pressure and the residue was crystallized from absolute ethanol. After 2 hours, 2.5 g. of colorless needles was obtained, m.p. 80–88°. The mother liquor on storage in a refrigerator for 2 days deposited about 0.05 g. of colorless platelets, m.p. 101°.

The infrared spectrum of the compound of m.p. 80–88° shows bands at 1760 and 1670 cm.$^{-1}$, attributable to the carbonyl stretching vibration of a γ-lactone and thiolester. The isomer melting at 101° has only the carbonyl absorption band at 1760 cm.$^{-1}$ for the γ-lactone (II, R = C_6H_5).

Symmetrical Diphenyl Dithiolphthalate.—Phthaloyl chloride (5.8 ml., 0.04 mole) in 25 ml. of benzene was added dropwise with mechanical stirring over a period of 2 hours to 8.2 ml. (0.08 mole) of thiophenol in a sodium methoxide solution, prepared from 1.74 g. of sodium and 50 ml. of absolute methanol. The colorless solid was collected by filtration and washed well with water. After drying in a vacuum desiccator for 12 hours there was obtained 13.2 g. (94%), m.p. 128–131°. An analytical sample was prepared by crystallizing twice from absolute ethanol; m.p. 130–130.6°.

Anal. Calcd. for $C_{20}H_{14}O_2S_2$: C, 68.57; H, 4.00; S, 18.29. Found: C, 68.54; H, 4.01; S, 18.46.

The infrared spectrum has only the band at 1670 cm.$^{-1}$ which may be assigned to the carbonyl absorption of a thiolester.

N,N′-Dibenzylphthalamide from Symmetrical Diphenyl Dithiolphthalate.—A solution of 0.60 ml. (5.48 mmoles) of distilled benzylamine, 0.96 g. (2.74 mmoles) of symmetrical diphenyl dithiolphthalate and 25 ml. of dioxane was stirred mechanically for 24 hours at 25°. The colorless solid was collected by filtration; 0.30 g. (32%), m.p. 173–175°. After evaporation of the dioxane under reduced pressure, the residue was crystallized from acetone, yielding 0.41 g. (43%) of colorless needles, m.p. 174–175°.

Anal. Calcd. for $C_{22}H_{20}N_2O_2$: C, 76.75; H, 5.82; N, 8.14. Found: C, 76.62; H, 5.93; N, 8.04.

Symmetrical Di-(*p*-nitrophenyl) Dithiolphthalate.—Phthaloyl chloride (3.2 ml., 0.0365 mole) in 20 ml. of acetone was added dropwise with mechanical stirring in 20 minutes to a solution of 4.5 g. (0.028 mole) of *p*-nitrothiophenol and 80 ml. of acetone. Pyridine (2.6 ml., 0.0365 mole) in 25 ml. of acetone was next added over a period of 55 minutes. After stirring at 25° for 18 hours, the precipitated brown solid was collected by filtration, washed with successive 100-ml. portions of water, 5% sodium bicarbonate and again with water. After drying in a vacuum desiccator there was obtained 4.6 g. (74.5%), m.p. 188–189.2°. An analytical sample (light-yellow needles) was prepared by two recrystallizations from benzene; m.p. 188–188.5°.

Anal. Calcd. for $C_{20}H_{12}N_2O_6S_2$: C, 54.55; H, 2.75; N, 6.36; S, 14.56. Found: C, 54.52; H, 2.90; N, 6.44; S, 14.75.

The infrared spectrum shows only the carbonyl absorption peak at 1670 cm.$^{-1}$ typical of a thiolester.

Ethyl Phthalimidoacetate from Symmetrical Di-(*p*-nitrophenyl) Dithiolphthalate.—Ethyl glycinate (0.346 g., 3.4 mmoles) in 20 ml. of methylene chloride was added dropwise to a solution of 1.0 g. (2.3 mmoles) or symmetrical di-(*p*-nitrophenyl) dithiolphthalate and 50 ml. of methylene chlo-

(11) The infrared spectra were determined with a Baird double beam recording spectrophotometer, model B, fitted with a sodium chloride prism. We are indebted to Dr. S. M. Nagy and his associates for the microanalyses, and to Dr. N. A. Nelson for the infrared measurements.

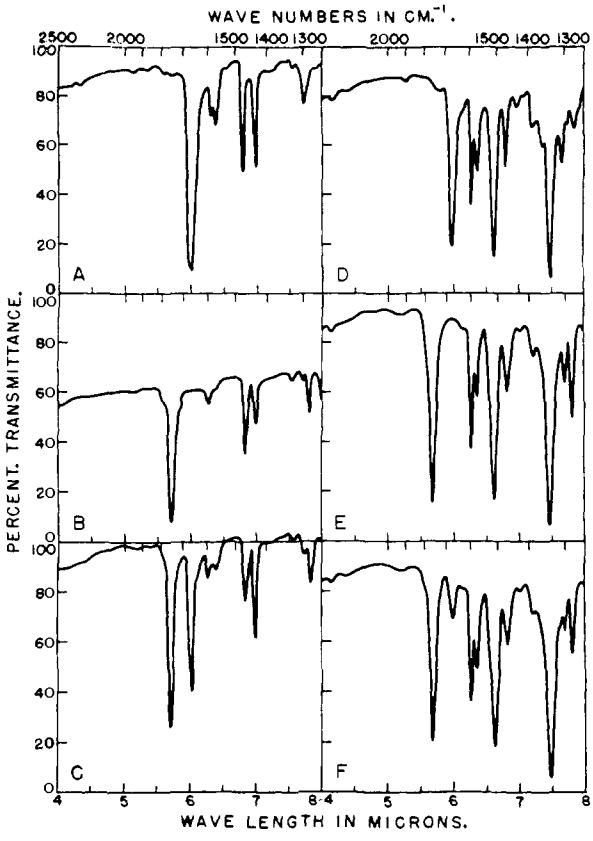


Fig. 1.—Infrared spectra: curve A, symmetrical diphenyl dithiolphthalate; curve B, unsymmetrical diphenyl dithiolphthalate; curve C, mixture of symmetrical and unsymmetrical diphenyl dithiolphthalate; curve D, symmetrical di-(*p*-nitrophenyl) dithiolphthalate; curve E, unsymmetrical di-(*p*-nitrophenyl) dithiolphthalate; curve F, mixture of symmetrical and unsymmetrical di-(*p*-nitrophenyl) dithiolphthalate. All spectra were determined in solid potassium bromide.

ride. The mixture was stirred mechanically at 25° for 18 hours. After the methylene chloride was removed by distillation under reduced pressure, the residue was taken up in 40 ml. of benzene and extracted with successive 40-ml. portions of 5% hydrochloric acid, 5% sodium bicarbonate and water. After drying and removal of the solvent, the residue was crystallized from 10 ml. of absolute ethanol; 0.40 g. (75%), m.p. 109–110°. One recrystallization raised the melting point to 112–113°.

The mixed melting point with authentic ethyl phthalimidoacetate was undepressed.

Treatment of Tryptophan Ethyl Ester with Symmetrical Di-(*p*-nitrophenyl) Dithiolphthalate.—Triethylamine (0.6 ml., 4.6 mmoles) in 20 ml. of methylene chloride was added dropwise with stirring to a solution of 0.66 g. (2.3 mmoles) of tryptophan ethyl ester hydrochloride and 0.50 g. (2.3 mmoles) of symmetrical di-(*p*-nitrophenyl) dithiolphthalate in 45 ml. of methylene chloride. The mixture was stirred for 12 hours at 25°. After the methylene chloride was evaporated under reduced pressure, the residue was taken up in 50 ml. of benzene and extracted successively with 50-ml. portions of water, 5% hydrochloric acid and finally again with water. After drying and removal of the solvent, the residue was crystallized from benzene; 0.60 g. (60%), m.p. 191–192.5°. An analytical sample was prepared by two recrystallizations from benzene.

Anal. Calcd. for $C_{20}H_{12}N_2O_6S_2$: C, 54.55; H, 2.75. Found: C, 54.46; H, 3.04.

The infrared spectrum has only the carbonyl stretching frequency at 1760 cm.$^{-1}$ characteristic of a γ-lactone.

The mixed melting point of I and II, R = *p*-$C_6H_4NO_2$, was 160–165° (depressed).

Treatment of Glycine with Symmetrical Di-(*p*-nitrophenyl) Dithiolphthalate.—A mixture of 0.85 g. (1.15 millimoles) of glycine, 0.50 g. (1.15 mmoles) of the symmetrical isomer I (R = *p*-$C_6H_4NO_2$), and 0.096 g. (1.15 mmoles) of sodium bicarbonate in a solution of 50 ml. of dioxane and 3.0 ml. of water was stirred at 25° for 18 hours. Hydrogen peroxide (0.30 ml. of 30%) was added with continued stirring for 1 hour. After the solvent was evaporated under reduced pressure, the residue was treated with 20 ml. of warm water and the yellow solid was collected by filtration. One recrystallization from benzene gave fine, yellow needles; 0.2 g. (40%), m.p. 191–192.5°. The aqueous filtrate was distilled under reduced pressure, the colorless solid remaining was recrystallized from water; 0.052 g. (24%), m.p. 193–194°.

The mixed melting point with authentic phthaloylglycine (m.p. 194°) was undepressed.

The infrared spectrum of the yellow, crystalline product shows only the band for the γ-lactone and a mixed melting point with the original symmetrical isomer was depressed.

Isomerization of I to II (R = *p*-$C_6H_4NO_2$).—A solution of 0.50 g. (1.14 mmoles) of symmetrical di-(*p*-nitrophenyl) dithiolphthalate and 3.0 ml. (1.14 mmoles) of triethylamine in 30 ml. of methylene chloride was stirred mechanically for 18 hours at 25°. The solution was extracted with two 30-ml. portions of 5% hydrochloric acid and once with 30 ml. of water. After drying, the methylene chloride was evaporated under reduced pressure and the residual yellow solid recrystallized from benzene; 0.15 g. (30%) of fine, yellow needles was obtained, m.p. 188–189°. The mixed melting point with starting material was undepressed. The infrared spectra were identical.

The benzene mother liquor, on storage in a refrigerator, for one week deposited 0.20 g. (40%) of yellow needles, m.p. 158–163°. The infrared spectrum has strong bands in the carbonyl absorption region corresponding to I (1670 cm.$^{-1}$) and II (1760 cm.$^{-1}$).

CAMBRIDGE 39, MASSACHUSETTS

[CONTRIBUTION FROM ABBOTT LABORATORIES]

Local Anesthetics. VI.[1] Alkamine Ethers of Alkyl Hydroxybenzoates

BY M. B. MOORE AND MAYNETTE VERNSTEN

RECEIVED JULY 5, 1956

The synthesis of alkamine ethers of the three isomeric series of hydroxybenzoic esters is reported. The lower alkyl esters have local anesthetic properties, and the higher esters are fungistatic.

Only a few carboalkoxyphenyl alkamine ethers have been reported in the literature[2] and none of these include cyclic aminoalkyl ethers. In view of the advantages of the 4-morpholinyl group in aminoalkyl aryl ethers,[1] it appeared desirable to study its effect when combined with a carboalkoxy on the ring. The lower members first prepared were shown to exhibit local anesthetic effect, and

(1) Paper V, THIS JOURNAL, **76**, 4396 (1954).

(2) (a) C. Rohmann and A. Koch, *Arch. Pharm.*, **276**, 154 (1938); (b) R. Fusco, S. Chiavarelli, G. Palazzo and D. Bovet, *Gazz. chim. ital.*, **78**, 951 (1948); *C. A.*, **43**, 6592a (1949).