The method has extremely high sensitivity, being operable below the microgram level, and has the inherent specificity and accuracy characteristic of isotope techniques.

Recoveries of added amounts of glycine, alanine and proline from a mixture of twelve synthetic amino acids are reported to demonstrate the accuracy and specificity of the analytical procedure.

Values are reported for the glycine, alanine and proline contents of the crystalline proteins β-lactoglobulin, human hemoglobin, aldolase and phosphoglyceraldehyde dehydrogenase.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TENNESSEE AGRICULTURAL & INDUSTRIAL STATE COLLEGE]

Preparation and Reactions of Several Chlorine Substituted Phenoxyacetyl Chlorides

BY CARL M. HILL, MYRON B. TOWNS AND GILBERT SENTER

Chemical investigation involving study of the several phenoxy acetic acids and their derivatives has been chiefly concerned with their insecticidal and herbicidal activity. Of the six phenoxy substituted acetic acids (phenoxy, 2-chlorophenoxy, 4-chlorophenoxy, 2,4-dichlorophenoxy, 2,4,5-trichlorophenoxy and 2,4,6-trichlorophenoxy) the derivatives of the two trichloro acids described in this paper are not reported in the literature. It was of interest, therefore, to investigate the preparation and properties of these derivatives and to establish their identification.

Inasmuch as the phenyl esters (except phenyl phenoxyacetate) of the six acids mentioned above are not described in the literature, these were prepared and identified.

Experimental

Acids.—The 2,4,5- and 2,4,6-trichlorophenoxyacetic acids were obtained from Dow Chemical Company and were purified by recrystallization from chloroform; 2,4,5-trichlorophenoxyacetic acid, m. p. 152–153° (uncor.) (lit.,[1] m. p. 154–55°), neut. equiv. calcd. for $C_8H_5O_3Cl_3$ 255.5, found, 257.7; 2,4,6-trichlorophenoxyacetic acid, m. p. 177–178° (uncor.), (lit.,[1,2] m. p., 190°, 177°), neut. equiv. found 256.0.

2,4,5-Trichlorophenoxyacetyl Chloride.—Into a round-bottomed flask equipped with a condenser set for reflux was placed 64 g. of 2,4,5-trichlorophenoxyacetic acid. One hundred and nineteen grams of purified thionyl chloride were added dropwise to the acid over a period of twenty-four hours. At the end of this time, the reaction mixture was refluxed on a steam-bath for two hours. The excess thionyl chloride was removed by distillation at atmospheric pressure. Distillation of the residue from a modified Claisen flask, under reduced pressure, gave 54.8 g. (80.0%) of 2,4,5-trichlorophenoxyacetyl chloride; b. p. 165–167° (6 mm.). This product was a waxy, white solid with a cocoanut-oil odor; m. p., 78–79° (uncor.).

Anal. Calcd. for $C_8H_4O_2Cl_4$: ionizable Cl, 12.94. Found: Cl, 12.46.

2,4,6-Trichlorophenoxyacetyl Chloride.—This compound was prepared by the method described for 2,4,5-trichlorophenoxyacetyl chloride using 64 g. of 2,4,6-trichlorophenoxyacetic acid; yield 61.6 g. (90.0%). This product was a waxy, white solid; b. p. 147–150° (5 mm.), m. p., 55–56° (uncor.).

Anal. Calcd. for $C_8H_4O_2Cl_4$: ionizable Cl, 12.94. Found: Cl, 13.03.

Both chlorides were analyzed for ionizable chlorine according to the following procedure: Fifty ml. of ethanol, 15 ml. of 2 *M* potassium hydroxide and 0.5 g. of the acid chloride were refluxed for twenty minutes in an erlenmeyer flask attached to a water-cooled condenser. The solution was allowed to cool, after which 50 ml. of distilled water was added through the head of the condenser. The solution was transferred to a 400-ml. beaker and the washings from the flask were added. After acidifying the solution with 1:1 nitric acid, the chlorine was precipitated with 0.5 *M* silver nitrate. The solution was then heated, with stirring, and the precipitated silver chloride filtered. The precipitate was washed on filter with 1:1 nitric acid followed by ethanol, dried and weighed as silver chloride.

Amides

2,4,5-Trichlorophenoxyacetamide.—To 0.5 g. of 2,4,5-trichlorophenoxyacetyl chloride was added a slight excess of concentrated ammonia and the mixture heated over a water-bath until precipitation of the amide was complete. The crude amide was filtered and recrystallized from dilute ethanol. The pure product was a white solid; m. p. 173–174° (uncor.), yield 0.50 g. (97.5%).

Anal. Calcd. for $C_8H_6O_2Cl_3N$: N, 5.50. Found: N, 5.81.

2,4,6-Trichlorophenoxyacetamide.—This amide was prepared in the manner described for the 2,4,5-trichlorophenoxyacetamide, starting with 0.5 g. of 2,4,6-trichlorophenoxyacetyl chloride. This product was a white crystalline solid; m. p. 195–196° (uncor.), yield 0.50 g. (98.0%).

Anal. Calcd. for $C_8H_6O_2Cl_3N$: N, 5.50. Found: N, 5.59.

Ethyl Esters

Ethyl 2,4,5-Trichlorophenoxyacetate.—To 5 g. of 2,4,5-trichlorophenoxyacetyl chloride was added a slight excess of 95% ethanol. The mixture was heated under reflux for two hours, allowed to cool, and washed with a saturated solution of sodium bicarbonate and then with water. The crude ester was extracted with diethyl ether and the ethereal solution dried over anhydrous calcium chloride. After removal of the ether, the crude ester was recrystallized from dilute ethanol. This product was a white crystalline solid; m. p. 63–64° (uncor.), yield 5.1 g. (89%), sap. equiv. calcd. for $C_{10}H_9O_3Cl_3$ 283.6, found 281.0.

Ethyl-2,4,6-Trichlorophenoxyacetate.—Five grams of 2,4,6-trichlorophenoxyacetyl chloride was used; yield 2.8 g. (85%). This ester was a white crystalline solid; m. p. 33–34° (uncor.), sapn. equiv. found, 280.0.

Anilides

2,4,5-Trichlorophenoxyacetanilide.—A solution of 5 g. of 2,4,5-trichlorophenoxyacetyl chloride and 15 ml. of chloroform was placed in an erlenmeyer flask. To this was added a slight excess of pure aniline. The reaction mixture was heated under reflux for thirty minutes and then allowed to cool. The crude anilide was filtered off

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(1) Synerholm and Zimmerman, *Contrib. Boyce Thompson Institute*, **14**, 91 (1945); *Chem. Abst.*, **39**, 1474 (1946).

(2) Haskelberg, *J. Org. Chem.*, **12**, 426 (1947).

and recrystallized from dilute ethanol. This pure anilide was a white crystalline compound; m. p. 176–177° (uncor.), yield 4.4 g. (67%).

Anal. Calcd. for $C_{14}H_{10}O_2Cl_3N$: N, 4.25. Found: N, 4.52.

2,4,6-Trichlorophenoxyacetanilide.—This compound was prepared according to the procedure described for 2,4,5-trichlorophenoxyacetanilide using 5 g. of the corresponding acyl chloride. This anilide was a white crystalline solid; m. p. 107–108° (uncor.), yield 4.1 g. (63%).

Anal. Calcd. for $C_{14}H_{10}O_2Cl_3N$: N, 4.25. Found: N, 4.20.

Phenyl Esters

Phenyl Phenoxyacetate.[3]—To 5 g. of phenoxyacetyl chloride in an erlenmeyer flask was added dropwise an alkaline solution containing an equivalent amount of phenol dissolved in 10% sodium hydroxide. The reaction mixture was heated over a steam-bath for thirty minutes and then cooled. The ester crystallized out and was purified by recrystallization from dilute ethanol. The white crystalline product melted at 56–57° (uncor.); yield 5.0 g. (73%), sapn. equiv. calcd. for $C_{14}H_{12}O_2$ 228.0, found 224.0.

Phenyl 2-Chlorophenoxyacetate.—This phenyl ester was prepared from the corresponding acyl chloride according to the procedure described for phenyl phenoxyacetate. Five grams of the acyl chloride gave 4.9 g. (80%) of phenyl 2-chlorophenoxyacetate, a white crystalline solid; m. p., 58–59° (uncor.); sapn. equiv. calcd. for $C_{14}H_{11}O_3Cl$, 262.7, found, 262.2.

Phenyl 4-Chlorophenoxyacetate.—Used 5 g. of 4-chlorophenoxyacetyl chloride. This phenyl ester melted at 73–74° (uncor.); yield, 4 g. (63.5%); sapn. equiv. calcd. for $C_{14}H_{11}O_3Cl$, 262.7, found, 276.0.

Phenyl 2,4-Dichlorophenoxyacetate.—This compound was prepared from 5 g. of 2,4-dichlorophenoxyacetyl chloride by the method described for phenyl phenoxyacetate. Recrystallization of the ester from dilute ethanol gave 5.1 g. (82%) of product; m. p., 100–101° (uncor.); sapn. equiv. calcd. for $C_{14}H_{10}O_3Cl_2$ 297.2, found 301.5.

Phenyl 2,4,5-Trichlorophenoxyacetate.—A solution of 5 g. of the acyl chloride and an equivalent amount of phenol dissolved in 10% sodium hydroxide was treated as described for the preparation of phenyl phenoxyacetate. Recrystallization from dilute ethanol gave 4 g. (70%) of white crystalline product; m. p., 116–117° (uncor.), sapn. equiv. calcd. for $C_{14}H_9O_3Cl_3$ 331.6, found 336.0.

Phenyl 2,4,6-Trichlorophenoxyacetate.—Five grams of 2,4,6-trichlorophenoxyacetyl chloride and an equivalent amount of phenol were used in alkaline solution. The resulting phenyl ester was recrystallized from dilute ethanol. The yield of ester was 4.5 g. (75%); m. p. 84.5–85° (uncor.), sapn. equiv. found 332.0.

Determination of the saponification equivalents of the six phenyl esters presented several experimental difficulties. Because of the formation of phenol upon acidification of the hydrolytic mixture, certain experimental errors were introduced which rendered the usual procedure employed for determination of saponification equivalents inaccurate and unreliable.

Therefore, the following procedure was employed. An accurately weighed sample (0.2 to 0.5 g.) of the phenyl ester was introduced into an erlenmeyer flask and a measured excess of 0.25 *N* sodium hydroxide solution added. The flask was then attached to a water cooled condenser and the mixture refluxed for six to eight hours or until the ester disappeared. At the end of this time, the mixture was allowed to cool and a calculated excess of 0.25 *N* hydrochloric acid was added from a buret. At this point the total volume of the mixture was noted. The excess acid was then backtitrated with standard alkali to the end point of phenolphthalein as indicator.

The titration error due to the production of phenol was corrected by weighing out the theoretical amount of pure phenol as was present in the weighed sample of phenyl ester, and preparing an aqueous solution of the same molar concentration and volume as that of the saponification mixture after addition of the excess standard acid. The aqueous phenolic solution was then titrated with 0.25 *N* sodium hydroxide solution to the end point of phenolphthalein. The number of milliequivalents thus obtained was subtracted from the total number of milliequivalents of standard alkali used in saponification of the phenyl ester.

Summary

The preparation of 2,4,5- and 2,4,6-trichlorophenoxyacetyl chlorides from the corresponding acids has been reported. The reaction of these acyl chlorides with ammonia, aniline, ethanol and phenol has been investigated.

The phenyl esters chlorophenoxy-, 2-chlorophenoxy-, 4-chlorophenoxy-, 2,4-dichlorophenoxy-, 2,4,5-trichlorophenoxy- and 2,4,6-trichlorophenoxy acetate were prepared.

Several new compounds were prepared and identified.

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[3] Morel, *Bull. soc. chim.*, [3] **21**, 967 (1899); m. p. 58°.

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The Preparation and Properties of Some Branched-Chain Alkyl Bromomethyl Ethers

BY HAROLD W. LUCIEN[1] AND CLARENCE T. MASON[2]

The importance of the halomethyl ethers as intermediates in synthesis, and the greater reactivity of the bromomethyl ethers[3] make necessary the present investigation to extend the knowledge of the branched-chain bromomethyl ethers.

The Henry synthesis and its modifications[4–7] are carried out by saturating equimolar quantities of an alcohol–aldehyde mixture with a hydrogen halide. In the present work branched-chain bromoethers were prepared by the Henry synthesis,[4] Wedekind's adaptation,[7] and two new modifications of Henry's method. When pre-

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[1] A part of this article is taken from the thesis presented to the graduate faculty of Tuskegee Institute by Harold W. Lucien, in partial fulfillment of the requirement for the degree of Master of Science. Presented at the September, 1948, Meeting of the American Chemical Society, St. Louis, Mo.

[2] Director of Research, George W. Carver Foundation, Tuskegee Institute, Alabama.

[3] Hamonet, *Compt. rend.*, **138**, 814 (1904).

[4] Henry, *Bull. acad. roy. Belg.*, [3] **25**, 439 (1938).

[5] Karvonen, *Acad. sci. Fennicae*, **3A**, 1 (1912); *C. A.*, **14**, 2175 (1920).

[6] Blair and Henze, THIS JOURNAL, **54**, 399 (1932).

[7] Wedekind, German patent 135,310, Aug. 31, 1901; *Chem. Zentr.*, **73**, II, 1164 (1902).