yielded 8.35 g. of *n*-octyl alcohol (64.1%, b.p. 48-50° at 0.5 mm., $n^{23}\text{D}$ 1.4288; lit.[9] 98° at 19 mm., $n^{20.5}\text{D}$ 1.4303), 2.9 g. of 3-(*n*-octyloxy)-propionitrile (15.8%, b.p. 84-87° at 0.5 mm., $n^{23}\text{D}$ 1.4329; lit.[1] b.p. 152-153° at 20 mm., $n^{24}\text{D}$ 1.4324) and 0.6 g. of residue.

The aqueous phase from the above separation was made alkaline in the presence of 100 ml. of ether and extracted three times with 50-ml. portions of ether. After drying over sodium sulfate, distillation of the ether extracts yielded 1.0 g. of 3-(*n*-octyloxy)-propylamine (5.3%, 68-70° at 0.5 mm., $n^{24}\text{D}$ 1.4388; lit.[1] 101° at 1 mm., $n^{24}\text{D}$ 1.4383) and 1.4 g. of residue. The recovery of identified products was 85.2%.

ABERDEEN PROVING GROUND, MD.

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[9] I. Heilbron, "Dictionary of Organic Compounds," Vol. IV, Oxford University Press, New York, N. Y., 1953.

[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

The Syntheses of Radioactive *o*- and *m*-Chloroacetanilide-Cl^{36}[1]

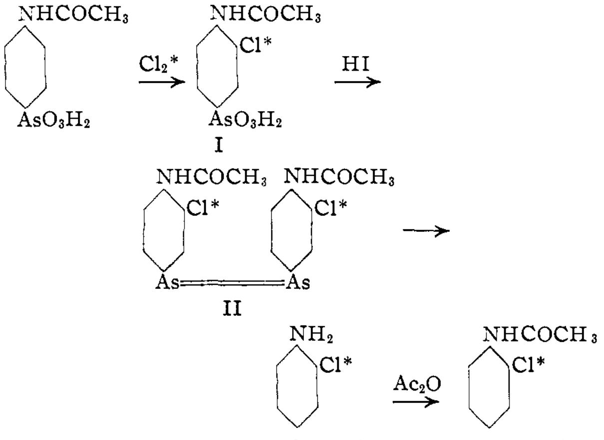
BY MARJORIE P. NEWELL,[2] MARY F. ARGUS AND FRANCIS E. RAY

RECEIVED JULY 13, 1956

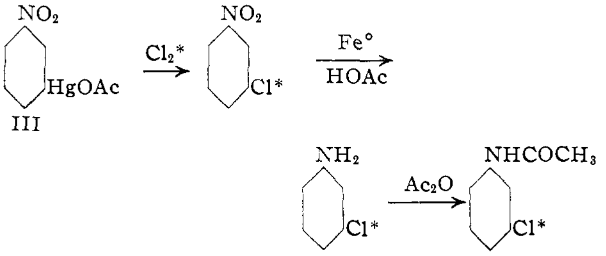
The syntheses of *o*- and *m*-chloroacetanilide-Cl^{36} have been accomplished *via* the chlorination of N-acetylarsanilic acid and *m*-nitrobenzenemercuric acetate, respectively.

To extend comparative studies of the distribution and metabolism of carcinogenic and non-carcinogenic amines and the effect of position substitution on this metabolism, the syntheses of radioactive *o*- and *m*-chloroacetanilide-Cl^{36} were undertaken.[3,4] The Sandmeyer reaction, which is the laboratory synthesis of choice for these compounds, was closed to us since this reaction requires a great excess of chloride ions that would dilute the chlorine-36. We sought syntheses, therefore, that gave better yields based on chlorine.

In developing a synthesis for *o*-chloroacetanilide-Cl^{36} we first used the sulfonic acid and nitro groups to block the *para* position. The removal of the sulfonic group was not accomplished easily and the replacement of the nitro group was accompanied by formation of phenols; hence, we prepared *o*-chloroacetanilide-Cl^{36} by direct chlorination of N-acetylarsanilic acid with subsequent reduction of the arsonic group with hydriodic acid.



In the preparation of *m*-chloroacetanilide-Cl^{36}, it was found that direct chlorination of *m*-nitrobenzene required a catalyst and that this catalyst combined with the unexpendable radioactive chloride ions. Replacement of the carboxyl group of the silver salt of *m*-nitrobenzoic acid by chlorine was also attempted unsuccessfully. We found, however, that *m*-chloronitrobenzene-Cl^{36} could be prepared readily by chlorination of *m*-nitrobenzenemercuric acetate. Reduction of the nitro group followed by acetylation of the amine yielded the desired *m*-chloroacetanilide-Cl^{36}.



Experimental[5]

Preparation of *o*-Chloroacetanilide-Cl^{36}. ***o*-Chloro-N-acetylarsanilic Acid-Cl^{36} (I).**—Five and two-tenths grams of N-acetylarsanilic acid (0.02 mole) was suspended in 70 ml. of glacial acetic acid and heated to boiling in a modification of Bertheim's method[6] of preparing *o*-chloro-N-acetylarsanilic acid. Chlorine gas (0.04 mole) was obtained in the following manner. Two generators were set up in series to provide the best utilization of the radioactive chlorine. The first generator contained 0.02 mole of active hydrochloric acid (200 μc.) plus 0.02 mole of inactive 6 *N* hydrochloric acid. This acid was oxidized to Cl_2^{36} with permanganate as previously described[3] and was conducted through a drying tube into the suspension of N-acetylarsanilic acid. The Cl_2^{36} generator was swept out with 0.02 mole of inactive chlorine gas from the second generator. The entire system was then swept out with carbon dioxide. As gassing proceeded, the suspension of N-acetylarsanilic acid dissolved completely leaving a clear pale amber solution. This solution was evaporated under reduced pressure at 55-60°. The product was washed twice with water and dried overnight.

Anal. Calcd. for $C_8H_9O_4AsClN$: Cl, 12.1. Found: Cl, 12.3.

o-Chloroaniline-Cl^{36}.—Three and nine-tenths gram of *o*-chloro-N-acetylarsanilic acid-Cl^{36} was suspended in 50 ml. of water in a 200-ml. three-necked flask fitted with a thermometer, stirrer, and condenser with gas trap attached. Stirring was begun and eight molar portions (0.104 mole, 13.68 ml.) of 57% HI was added through the reflux con-

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[1] Supported by Contract AT(40-1)1403 with the Atomic Energy Commission.

[2] Part of this paper is from the thesis by Marjorie P. Newell submitted in partial fulfillment of the requirements for the degree of Master of Science, University of Florida, August, 1954.

[3] J. M. Gryder, M. F. Argus, M. P. Newell and F. E. Ray, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 667 (1954).

[4] F. E. Ray, J. M. Gryder and M. F. Argus, *Proc. Am. Assoc. Cancer Research*, **1**, 39 (1954).

[5] All melting points uncorrected.

[6] A. Bertheim, *Ber.*, **43**, 529 (1910).

denser over a period of one hour while the temperature was slowly brought to 100°.[7] The reaction mixture was held at this temperature for 5–6 hr. During the reduction of *o*-chloro-N-acetylarsanilic acid to *o*-chloroaniline purple fumes of iodine were observed. The reaction mixture became very dark, all starting material went into solution, and metallic arsenic appeared to be present. It was noted during base runs that if an excessive amount of hydriodic acid was available, an iodinated crystalline compound was formed. If, on the other hand, just the six molecular proportions theoretically needed to remove the arsonic group was added, reduction was incomplete. This is undoubtedly a stepwise reaction with an arseno compound, 2,2′-dichloro-N,N′-diacetyldiaminoarsenobenzene (II) being formed as intermediate, and the acetyl group being removed before removal of the arseno group. After complete reduction the reaction mixture was made alkaline with an excess of saturated sodium hydroxide and steam distilled. *o*-Chloroaniline-Cl^{36} came over as a slightly yellowish oil.

***o*-Chloroacetanilide-Cl^{36}.**—The distillate containing *o*-chloroaniline-Cl^{36} was saturated with sodium chloride and twice extracted with benzene. The benzene solution was distilled off after acetylation of the compound with acetic anhydride. The product was recrystallized to radioactive purity[8] in 50% ethanol to a specific activity of 105,000 d./m./mg. Final yield of *o*-chloroacetanilide-Cl^{36} was 0.92 g., m.p. 88°.[9] The yield was 27% based on N-acetylarsanilic acid and 43.8 μc. or 21.9% of the original radioactivity was incorporated.

Preparation of *m*-Chloroacetanilide-Cl^{36}. *m*-Nitrobenzenemercuric Acetate (III).—*m*-Nitrobenzenemercuric acetate was prepared from the sodium salt of *m*-nitrosulfinic acid[10] in a modification of Kharasch and Chalkley's preparation of *m*-nitrobenzenemercuric chloride.[11]

***m*-Chloronitrobenzene-Cl^{36}.**—Five and one-tenth grams (0.0135 mole) of *m*-nitrobenzenemercuric acetate, m.p. 173°, dissolved in 25 ml. of glacial acetic acid kept at 80–90° was gassed slowly with Cl_2^{36} (0.027 mole). Two hundred μc. of chlorine-36 was used in this preparation. The radioactive hydrochloric acid was oxidized to Cl_2^{36} in the first generator and swept out with inactive Cl_2 from the second generator as described for the preparation of *o*-chloroacetanilide. The reaction mixture was left to stand overnight, neutralized with sodium hydroxide and steam distilled. Crystalline *m*-chloronitrobenzene-Cl^{36}, m.p. 45°,[12] was collected.

***m*-Chloroaniline-Cl^{36}.**—The *m*-chloronitrobenzene-Cl^{36} was reduced by refluxing 5 hr. with 40 ml. of 60% acetic acid and 2 g. of powdered iron. The mixture was made alkaline with saturated sodium hydroxide and steam distilled. *m*-Chloroaniline-Cl^{36} came over as a pale yellow oil.

***m*-Chloroacetanilide-Cl^{36}.**—*m*-Chloroaniline-Cl^{36} was twice extracted with benzene and acetylated with acetic anhydride. Recrystallization to radioactive purity from 25% ethanol yielded 1.1 g. of *m*-chloroacetanilide-Cl^{36} m.p. 73°[9] (yield 48.5% based on *m*-nitrobenzenemercuric acetate). Specific activity of the purified compound was 77,000 d./m./mg.; 38μc., or 19% of the original activity, was utilized.

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[7] G. W. Raiziss and J. L. Gavron, "Organic Arsenical Compounds," Reinhold Publ. Corp. Inc., (Chemical Catalog Co.) New York, N. Y., 1923, p. 151.

[8] J. L. Wood and H. R. Gutmann, *J. Biol. Chem.*, **179**, 535 (1949).

[9] F. Beilstein and A. Kurbatow, *Ann. Chem.*, **182**, 94 (1876).

[10] H. Limpricht, *Ber.*, **25**, 75, 3477 (1892).

[11] M. S. Kharasch and L. Chalkley, THIS JOURNAL, **43**, 611 (1921).

[12] W. W. Hartman and M. R. Brethen, "Organic Syntheses," Coll. Vol. I, H. Gilman, Editor, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 156.

GAINESVILLE, FLORIDA

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF ORGANIC DIVISION AND THE CHEMICAL RESEARCH DEPARTMENT, RESEARCH AND ENGINEERING DIVISION, MONSANTO CHEMICAL COMPANY]

N-Substituted-amides[1]

BY ARTHUR H. SCHLESINGER AND ERHARD J. PRILL

RECEIVED MAY 7, 1956

The synthesis of various N-substituted-amides, R–$CONR_1R_2$ is described. The novel formation of 2,2′-oxybis-(phenyl-

$$\begin{matrix}ArCHCONR_1R_2\\ |\\ O\\ |\\ ArCHCONR_1R_2\end{matrix}$$

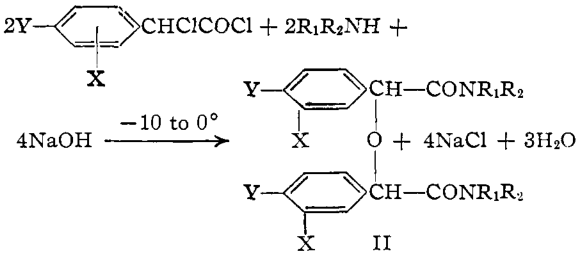
acetamides) from certain 2-chlorophenylacetyl chlorides under conditions normally expected to give 2-chlorophenylacetamides is discussed. The amides described failed to show appreciable phytotoxicity.

N-Substituted-2-chloroacetamides have shown high herbicidal activity.[2] As a continuation of the study of the relationship of structure to phytotoxicity, a large number of unreported chloroacyl amides have been synthesized.

The amides of Tables I–IV were prepared by the reaction of equivalent amounts of acid chlorides and amines in the presence of aqueous sodium hydroxide at −10 to 0°, usually in a solvent such as *sym*-tetrachloroethane or 1,2-dichloroethane. The low temperature was employed in order to reduce the possibility of hydrolysis of aliphatic chlorine atoms and/or elimination of HCl from many of the resultant chloro-N-substituted-amides.

$$R{-}COCl + R_1R_2NH + NaOH \longrightarrow R{-}CONR_1R_2 + NaCl + H_2O \quad \text{I}$$

While attempting to prepare 2-chlorophenylacetamides of structure I (R = C_6H_5CHCl–), the previously unreported 2,2′-oxybis-(N-substituted-phenylacetamides) (II) listed in Table V were obtained as the sole products.



The transformation of a benzyl type chlorine atom in the α-position into a benzyl type ether is usually accomplished under more strenuous conditions

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[1] Presented before the 130th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 16–21, 1956.

[2] P. C. Hamm and A. J. Speziale, Abstracts 127th National Meeting, American Chem. Soc., Cincinnati, O., March 30–April 2, 1955.