***m*-Aminobenzoylurea.**—The necessary *m*-nitrobenzoylurea was prepared by boiling the acid chloride and urea in benzene for 12 hours instead of following Griess' method[1] of fusing the components at 150°. The amino urea was obtained in the same way as the *o*-isomer, except that it was necessary to evaporate the alcohol before the substance separated completely on cooling. The yield was 6 g. from 10 g. of the nitro compound. As Griess' description of *m*-aminobenzoylurea is not complete, the following is appended: When rapidly heated it melts with gas evolution at about 210°, resolidifying and then remelting at about 275–80°. It is readily diazotized, in contradistinction to the *o*-isomer, yielding a scarlet color with R-salt, and dissolves readily in boiling water or 95% alcohol.

Kjeldahl: 0.0997 g. subst.; 16.50 cc. 0.1 *N* HCl.
Calcd. for $C_8H_9O_2N_3$: N, 23.46%. Found: N, 23.18%.

NEW YORK CITY.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.]

METHODS FOR THE ACYLATION OF AROMATIC AMINO COMPOUNDS AND UREAS, WITH ESPECIAL REFERENCE TO CHLOROACETYLATION.

BY WALTER A. JACOBS AND MICHAEL HEIDELBERGER.

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The importance of the halogenacetyl compounds has been demonstrated by their frequent use in organic synthesis. The great reactivity of the halogen atom has permitted their use in practically all the reactions in which alkyl halides have been employed. In the work of the authors on the quaternary salts of hexamethylenetetramine[2] one phase of their usefulness in synthetic work in chemotherapy was demonstrated. In continuing our work along similar lines we have had occasion to prepare the chloroacetyl derivatives of a large number of aromatic amino compounds of such widely differing constitution and solubility relationships that the older acylation methods frequently proved inapplicable.

The well-known Schotten-Baumann method has been quite successfully applied in the past to chloroacetylation. In the case of amino compounds soluble in water or alkali the conditions are simple, although, owing to the great reactivity of chloroacetyl chloride with aqueous alkali, a considerable excess of the chloride is usually required to furnish a satisfactory yield. In the case of bases insoluble in water, the use of neutral organic solvents usually proves of service, either in connection with

[1] Griess, *Ber.*, 8, 222 (1875).

[2] *J. Biol. Chem.*, 20, 685; 21, 103, 145, 403, 455, 465 (1915); *J. Exp. Med.*, 23, 563, 577 (1916).

aqueous alkali, or using an additional equivalent of the base to take up the hydrochloric acid set free. In both cases the method fails with insoluble compounds, while the latter modification is open to the objection that the entire quantity of amine cannot be chloroacetylated in a single operation. The use of pyridine, an excellent solvent for many acylations, does not yield good results when chloroacetyl chloride is to be used. We therefore feel that the method outlined below is the most generally satisfactory where chloroacetyl derivatives are in question, and it is here presented not only with this view, but also in the belief that its wide applicability will render it of more general service.

The essential principle of the method is the combined use of dilute acetic acid as solvent and sodium acetate as a buffer to remove the hydrochloric acid formed during the reaction. In such a system the amino compound is held in solution by the acetic acid, which is too feebly acidic to inhibit the specific reactivity of the acid chloride for the amino group. And this is far greater than the rate of hydrolysis of the acid chloride to the acid. As a result, the yields obtained are generally excellent. Acetic acid has, of course, frequently been employed as a solvent in acylations, and the use of sodium acetate to take the place of alkali is also on record, but we have been unable to find a reference to the obvious possibility of their combination.

In the majority of instances 50% acetic acid or, more specifically, a mixture of equal volumes of glacial acetic acid and saturated sodium acetate solution, was found to be most generally serviceable as the solvent, and in but few cases was it necessary to make any change, such as the use of higher concentrations, or the addition of acetone. The method is, of course, inapplicable in cases of insolubility in acetic acid, as, for example, the aromatic amino acids, but where solubility permits, it is our belief that the procedure here described is more satisfactory than the hitherto available methods, not only on account of its wide applicability and its simplicity, but also because the process is carried out in a homogeneous aqueous solution from which the acyl compound separates in practically pure form.

The method was found to be equally satisfactory for benzoylation with benzoyl chloride and for phenylchloroacetylation with phenylchloroacetyl chloride, and it can undoubtedly be extended to include other acid chlorides.

In passing from the amines to the ureas a different set of conditions must be taken into account. The substituted aromatic ureas, $RC_6H_4NHCONH_2$, are exceptionally difficult to chloroacetylate, not only because of their sparing solubility in practically all solvents, but also on account of the relative difficulty with which the NH_2 group in the uramino radical reacts with acid chlorides. It has been the usual custom with the simpler and more soluble members of this group to heat them either with

the acid chlorides alone or dissolved in a boiling neutral solvent, from which the liberated hydrochloric acid is evolved. For many of the complex ureas these methods were found unsatisfactory, for although partial reactions occurred, it was practically impossible to separate the chloroacetyl compound from the unchanged urea. This difficulty was finally overcome by the use of chloroacetic acid as a solvent.

The well powdered urea was either dissolved or suspended in molten chloroacetic acid and treated with chloroacetyl chloride. In every case the reaction proceeded smoothly and completely, resulting in a pure product. The use of glacial acetic acid as a substitute for the chloroacetic acid is inadvisable owing to the danger of obtaining acetyl derivatives.

In the experimental part we have not attempted to describe all of the instances in which the above methods were employed, but have selected from our material certain examples to demonstrate their usefulness. A description of other chloroacetyl compounds will appear in later communications.

EXPERIMENTAL.

1. Chloroacetylation of Amines.

Unless otherwise stated, the following method was used for chloroacetylating the amino compounds mentioned below. The substance was dissolved in a mixture of five parts of glacial acetic acid and five parts of a saturated solution of sodium acetate, calculating cubic centimeters per gram of substance used. The mixture was warmed, if necessary, to effect complete solution, rapidly chilled in ice-water, and treated with small quantities at a time of one and one-half molecular equivalents of the acid chloride, with vigorous shaking or turbining and continuing cooling. The acyl derivative generally separated immediately, and was filtered off after short standing in the cold, washed with 50% acetic acid and water, and recrystallized from the appropriate solvent. The analyses were made and melting points taken after drying to constant weight *in vacuo*, at 100° over concentrated sulfuric acid wherever possible.

Chloroacetanilide.—The crude product obtained from 5 g. aniline was recrystallized from 50% alcohol, yielding 7.75 g. long, narrow, glistening plates which melted at 136–7°, in agreement with the description given in the literature.

Kjeldahl: 0.1601 g. subst.; 9.4 cc. 0.1 *N* HCl.
Calcd. for C_8H_8ONCl: N, 8.26%. Found: N, 8.22%.

***p*-Iodochloroacetylaniline,** p-$IC_6H_4NHCOCH_2Cl$.—An equal weight of recrystallized product was obtained. It separates from 95% alcohol as rods, many of which are branched and curved, melting at 191–4°, the melting point being unchanged by a subsequent recrystallization. The substance is soluble in cold acetone, hot toluene, hot 95% alcohol, and readily soluble in hot glacial acetic acid.

Kjeldahl: 0.2046 g. subst.; 7.0 cc. 0.1 *N* HCl.
Calcd. for C_8H_7ONClI: N, 4.74%. Found: 4.79%.

The compound was also prepared, though less advantageously, by the Schotten-Baumann method.

***m*-Chloroacetylaminophenol.**[1]—The reaction mixture was evaporated to dryness *in vacuo* and taken up with water. 22 g. *m*-aminophenol gave 33 g. of the chloroacetyl derivative, melting at 136–8° and agreeing, when recrystallized, with the other properties previously described. The yield far exceeds that obtained by the use of chloroacetic anhydride.

***p*-Chloroacetylaminophenol.**—The reaction mixture from 5 g. of commercial *p*-aminophenol was evaporated to dryness *in vacuo* and the residue taken up with water, filtered, washed with a little water, and recrystallized from 50% alcohol, using boneblack. The yield was 5.5 g. The Schotten-Baumann method gave a smaller yield. The substance may also be recrystallized from water, benzene, or chloroform, and forms rosets of glistening platelets which melt at 144.5–6° (corr.) with preliminary softening. An aqueous suspension gives a pale grayish color with ferric chloride.

Kjeldahl: 0.2001 g. subst.; 10.80 cc. 0.1 *N* HCl.
Calcd. for $C_8H_8O_2NCl$: N, 7.55%. Found: N, 7.56%.

***o*-Chloroacetylaminobenzamide.**—Addition of chloroacetyl chloride to the solution containing 5 g. *o*-aminobenzamide (see preceding paper) produced so thick a mass of the chloroacetyl derivative that it was found necessary to add an additional 50 cc. of 50% acetic acid before the rest of the chloride could be added. 6.5 g. of the product were obtained. Recrystallized from 95% alcohol, the substance forms silky hairs which melt at 183–4.5° with preliminary softening when rapidly heated to 180° and then slowly. It is soluble in acetone, less so in hot chloroform, and difficultly in hot benzene.

Kjeldahl: 0.2808 g. subst.; 26.2 cc. 0.1 *N* HCl.
Calcd. for $C_9H_9O_2N_2Cl$: N, 13.18%. Found: N, 13.08%.

The compound was also prepared, though in smaller yield, by dissolving 15.5 g. *o*-aminobenzamide in acetone and adding 10 cc. chloroacetyl chloride, with chilling and shaking, followed by the immediate addition to the thick mass of 50 cc. 10% sodium hydroxide solution, with continued shaking. The mixture was then diluted with water, acidified to congo red with hydrochloric acid and filtered. The yield was 16 g.

***m*-Chloroacetylaminobenzamide.**—In order to dissolve 5.5 g. *m*-aminobenzamide (anhydrous, see preceding paper) completely it was necessary to add an additional 50 cc. of 50% acetic acid to the original mixture of 25 cc. acetic acid and 25 cc. saturated sodium acetate solution. The yield of chloroacetyl derivative was 8 g. Recrystallized from 95%

[1] Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 132 (1915).

alcohol, the amide forms aggregates of minute crystals which melt with decomposition at about 215°. It is very difficultly soluble in water, benzene, acetone, chloroform, and cold 95% alcohol.

Kjeldahl: 0.2062 g. subst.; 19.35 cc. 0.1 *N* HCl.
Calcd. for $C_9H_9O_2N_2Cl$: N, 13.18%. Found: N, 13.14%.

The compound was also synthesized from *m*-aminobenzoic acid through the chloroacetyl derivative described in the next paragraph. This was converted into the acid chloride by the action of phosphorus pentachloride in benzene suspension on the water bath. Crystallization of the chloride was completed by the addition of ligroin, after which the product was filtered off, washed with ligroin, dissolved in chloroform, and converted into *m*-chloroacetylaminobenzamide by shaking the solution with concentrated ammonia.

***m*-Chloroacetylaminobenzoic Acid.**—14 g. *m*-aminobenzoic acid were suspended in 100 cc. benzene and heated 12 hours under a reflux condenser with 12 g. chloroacetyl chloride. The amino acid was gradually replaced by its chloroacetyl derivative. After recrystallization from 50% alcohol, 16 g. of the product were obtained. Recrystallized again from acetic acid, it forms aggregates of minute crystals melting with preliminary softening at 230–2° to a brown liquid, with gas evolution. The acid is less difficultly soluble in acetone than in the other usual solvents in the cold, and is soluble in dilute sodium carbonate solution.

Kjeldahl: 0.2573 g. subst.; 11.85 cc. 0.1 *N* HCl.
Calcd. for $C_9H_8O_3NCl$: N, 6.56%. Found: N, 6.45%.

Hexamethylenetetraminium Salt of *m*-Chloroacetylaminobenzamide.—5.4 g. of recrystallized chloroacetyl compound and 3.8 g. hexamethylenetetramine were boiled for one and one-half hours in 250 cc. acetone. The mixture gradually changed to a thick paste of delicate, felted needles. After letting stand another hour in a warm place the salt was filtered off, boiled again with 100 cc. acetone to remove any unchanged chloroacetyl compound present, filtered, and dried. The yield was 4.5 g. When rapidly heated to 165°, then slowly, the salt darkens and sinters, melting at 169–70° to a greenish tar which quickly decomposes with gas evolution and turns orange. It is soluble in cold water, hot absolute alcohol, and practically insoluble in chloroform or acetone.

0.1439 g. subst.; 0.0584 g. AgCl.
Calcd. for $C_{15}H_{21}O_2N_6Cl$: Cl, 10.05%. Found: Cl, 10.04%.

***p*-Chloroacetylaminobenzamide.**—3 g. *p*-aminobenzamide (see introduction, preceding paper) required the addition of 30 cc. of 50% acetic acid to the usual mixture of 15 cc. acetic and 15 cc. saturated sodium acetate solution before complete solution took place. The yield of chloroacetyl derivative was 4.5 g. Recrystallized from 95% alcohol, adding a few drops of aqueous ammonia to the hot solution to hold back any acid

present and cooling rapidly, the substance forms silky needles. When rapidly heated to 240° and then slowly, it melts and decomposes at 241–3°. It is less sparingly soluble in hot acetic acid than in the other usual solvents.

Kjeldahl: 0.1940 g. subst.; 18.50 cc. 0.1 *N* HCl.
Calcd. for $C_9H_9O_2N_2Cl$: N, 13.18%. Found: N, 13.36%.

The compound was also prepared as in the case of the *o*-isomer by the action of chloroacetyl chloride and aqueous sodium hydroxide in acetone, 15 g. of the aminobenzamide yielding only 14 g. of the chloroacetyl derivative.

***p*-Aminophenylacetamide.**—*p*-Aminophenylacetic acid (see preceding paper) was esterified with methyl alcohol and hydrochloric acid gas. 50 g. of the methyl ester hydrochloride were treated in the cold with 150 cc. concentrated ammonia solution and allowed to stand in a stoppered flask with occasional shaking. The oily ester gradually dissolved and the amide crystallized out. The yield was 30 g. Recrystallized from water, using bone-black to remove the slight color, it forms glistening scales, melting at 161–2° (corr.). Purgotti,[1] who prepared the amide by reducing the nitro compound with ammonium sulfide, reports the melting point as 153–4°.

Kjeldahl: 0.1695 g. subst.; 22.65 cc. 0.1 *N* HCl.
Calcd. for $C_8H_{10}ON_2$: N, 18.67%. Found: N, 18.72%.

***p*-Chloroacetylaminophenylacetamide.**—During the chloroacetylation of 20 g. of the amino compound the reaction mixture set to a thick mass. This was diluted with water, and the substance filtered off, washed, and dried. The yield was 24 g. Recrystallized first from 85% alcohol, then acetic acid, it forms thin, rectangular plates melting to a brown liquid at 191–1.5° (corr.), with slight preliminary softening. The compound is also soluble in hot alcohol, readily in hot acetic acid, practically insoluble in hot benzene, and difficultly soluble in cold acetone. It gives a strong halogen test.

Kjeldahl: 0.1439 g. subst.; 17.7 cc. 0.07 *N* HCl.
Calcd. for $C_{10}H_{11}O_2N_2Cl$: N, 12.37%. Found: N, 12.30%.

2. Phenylchloroacetylation.

The acylation method was next applied to the preparation of several phenylchloroacetyl derivatives, which are described below. The method used was the same as in the case of chloroacetyl chloride, except that one to one and one-tenth mols. of phenylchloroacetyl chloride[2] were used, a larger excess being unnecessary since the chloride does not react as readily with water as chloroacetyl chloride does. In every case the yield was practically quantitative.

[1] Purgotti, *Gazz. chim. ital.*, **20**, 598 (1890).

[2] Prepared according to Staudiger and Bereza, *Ber.*, **44**, 536 (1911).

***p*-Phenylchloroacetylaminophenylurea,** *p*-$PhCHClCONHC_6H_4NHCONH_2$.—15 g. *p*-aminophenylurea (see following paper) were dissolved in a mixture of 75 cc. acetic acid and 75 cc. saturated sodium acetate solution, cooled in ice-water, and treated with 19 g. phenylchloroacetyl chloride, with shaking and cooling. After dilution with water the precipitate was filtered off and washed with water. Recrystallized from 95% alcohol, with bone-blacking, the urea forms minute platelets and needles which, when rapidly heated to 195° and then slowly, melt and effervesce at 200–1°. It gives a strong Beilstein test and dissolves in boiling, dilute sodium hydroxide solution with a yellow color. It is practically insoluble in hot water or hot benzene, but soluble in hot 95% alcohol or acetone.

0.1372 g. subst.; 17.0 cc. N, 737 mm., 23.5°.
Calcd. for $C_{15}H_{14}O_2N_3Cl$: N, 13.84%. Found: N, 13.84%.

***m*-Phenylchloroacetylaminophenol,** *m*-$PhCHClCONHC_6H_4OH$.—5.5 g. *m*-aminophenol were dissolved in 55 cc. acetic acid and 55 cc. saturated sodium acetate solution. The mixture remained clear after addition of the phenylchloroacetyl chloride but deposited the acyl derivative after diluting with water and scratching. Recrystallized first from 50% alcohol, then from toluene, it forms aggregate of spindles which melt with preliminary softening and slow effervescence at 157–8°. It gives a strong Beilstein test and dissolves in dilute sodium hydroxide solution with a pale yellow color which changes to a transient purple on boiling. It is difficultly soluble in cold acetic acid, readily in hot, the solution treated with a drop of aqueous sodium nitrite and warmed at 100°, giving a deep red color.

Kjeldahl: 0.2050 g. subst.; 7.7 cc. 0.1 *N* HCl.
Calc. for $C_{14}H_{12}O_2NCl$: N, 5.36%. Found: N, 5.26%.

***m*-Phenylchloroacetylaminobenzamide,** *m*-$PhCHClCONHC_6H_4CONH_2$.—This substance crystallizes from the reaction mixture after dilution. The product obtained from 7.5 g. *m*-aminobenzamide and 11 g. acid chloride was boiled up with about 100 cc. 50% alcohol and filtered off hot in order to remove any of the more soluble impurities that might be present. Recrystallized from acetic acid, it separates as micro-platelets which are soluble in boiling 95% alcohol, difficultly soluble in acetone, and very sparingly so in boiling water. Rapidly heated to 210° and then slowly, it melts and decomposes at 218° with slight preliminary softening.

Kjeldahl: 0.1468 g. subst.; 10.0 cc. 0.1 *N* HCl.
Calc. for $C_{15}H_{13}O_2N_2Cl$: N, 9.71%. Found: N, 9.54%.

***p*-Phenylchloroacetylaminophenylacetamide,** *p*-$PhCHClCONHC_6H_4CH_2CONH_2$.—The precipitation of this substance from the reaction mixture obtained from 6 g. aminophenylacetamide and 8 g. chloride was completed by the addition of an equal volume of water. Recrystallized first from 50%, then from 95% alcohol it formed minute, thin plates

and needles melting at about 184.5–5.5° to a yellow liquid, the exact point of fusion depending somewhat on the rate of heating. A solution in hot water evolves ammonia when boiled with a few drops of sodium hydroxide solution and then reacts for chlorine ion. The substance is soluble in acetone, acetic acid, or hot 95% alcohol, and is practically insoluble in chloroform.

Kjeldahl: 0.1400 g. subst.; 9.35 cc. 0.1 *N* HCl.
Calc. for $C_{16}H_{15}O_2N_2Cl$: N, 9.26%. Found: N, 9.35%.

3. Benzoylation.

For comparison with the hitherto available methods of benzoylation several simple aromatic amines were benzoylated as in the case of the other acylations, using 1.1 mols. of benzoyl chloride. 5 g. each of aniline, α-naphthylamine, and β-naphthylamine gave, respectively, 8.8, 7, and 7.4 g. of the recrystallized benzoyl derivative, the purity of the product being controlled in each case by analysis and melting-point determination.

4. Chloroacetylation of Ureas.

The following method was used for the chloroacetylation of substituted aromatic ureas in a number of instances to be reported in a later paper, two examples being given below: The finely powdered urea was suspended in 3 parts of chloroacetic acid which had been melted on the water bath, after which 1.5 molecular equivalents of chloroacetyl chloride were added and the heating continued 15–30 minutes. Solution occurred rapidly as a rule, and after completion of the reaction the mixture was poured into water, well stirred, and the resulting precipitate of chloroacetyl derivative washed well with water.

***o*-Uraminophenyl Benzoate (*o*-Benzoyloxyphenylurea)**, *o*-$H_2NCONHC_6H_4OCOC_6H_5$.—20 g. *o*-uraminophenol were dissolved in 100 cc. pyridine, cooled in a freezing mixture, and carefully treated with 19 g. benzoyl chloride. After standing for one-half hour, the mixture was stirred into an excess of cold, dilute sulfuric acid and the precipitate filtered off, washed with water, and recrystallized from 50% alcohol. The yield was 27 g. Recrystallized again from 95% alcohol, the substance forms aggregates of minute spears which melt slowly at 178–9° (corr.). It is soluble in cold acetone, very difficultly so in boiling water, and almost insoluble in boiling benzene.

0.1481 g. subst.; 13.7 cc. N, 765 mm., 19.5°.
Calc. for $C_{14}H_{12}O_3N_2$: N, 10.93%. Found: N, 10.87%.

***o*-Chloroacetyluraminophenyl Benzoate**, *o*-$ClCH_2CONHCONHC_6H_4OCOC_6H_5$.—The reaction mixture was heated for only 15 minutes in this case. Recrystallized from acetic acid the benzoate forms voluminous rosets of silky hairs which readily become triboelectric and which are less sparingly soluble in acetone and ethyl acetate than in the other usual solvents in the cold. Rapidly heated to 215° and then slowly, it melts at

219° with gas evolution and slight preliminary softening. It gives a strong Beilstein test.

0.1315 g. subst.; 9.6 cc. N, 771 mm., 23.0°.
Calcd. for $C_{16}H_{13}O_4N_2Cl$: N, 8.43%. Found: N, 8.54%.

***m*-Uraminophenyl Benzoate.**—This substance was prepared in essentially the same way as the *o*-isomer. The yield obtained from 29 g. *m*-uraminophenol was 49 g., melting at 178–80°. Recrystallized twice from 95% alcohol, using bone-black, it forms lenticular plates which dissolve in acetone, boiling water, and very readily in boiling 95% alcohol. Rapidly heated to 175°, then slowly, the benzoate softens above 180° and melts slowly at 183–4° (corr.), a higher figure being obtained if the final heating is not slow.

0.1590 g. subst.; 14.8 cc. N, 767 mm., 22.5°.
Calcd. for $C_{14}H_{12}O_3N_2$: N, 10.93%. Found: N, 10.85%.

***m*-Chloroacetyluraminophenyl Benzoate.**—After 30 minutes' heating the reaction mixture was poured into ice-water, precipitating the substance as a gum which rapidly crystallized. 15 g. of the urea yielded 18 g. of crude product. Recrystallized first from hot acetone by the addition of an equal volume of water, then from 95% alcohol, the benzoate separates in rosets of long, flat needles which dissolve more readily in boiling acetic acid than in the other usual solvents. Rapidly heated to 185° and then slowly, it softens slightly and melts at 188–9.5° to a brown liquid, with slight gas evolution.

0.1591 g. subst.; 11.7 cc. N, 746 mm., 22.5°.
Calc. for $C_{16}H_{13}O_4N_2Cl$: N, 8.43%. Found: N, 8.34%.

NEW YORK CITY.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.]

UNSYMMETRICAL DERIVATIVES OF AROMATIC DIAMINES.

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In the course of our synthetic work it was found necessary to prepare a number of derivatives of *m*-phenylenediamine, *p*-phenylenediamine, and 2,4-tolylenediamine. It was soon found that, although a great many of the simpler unsymmetrical derivatives of these amines had been made, notably by Schiff and Vanni[1] and Schiff and Ostrogovich,[2] previous workers had been unable to isolate all of these substances in a state of purity or else had recorded properties which we were unable to confirm. For example, Schiff and Ostrogovich state that *p*-aminophenylurea is an easily oxidizable substance melting at 129°, whereas all our preparations

[1] Schiff and Vanni, *Ann.*, **268**, 305 (1892).
[2] Schiff and Ostrogovich, *Ibid.*, **293**, 371 (1896).