cous liquid and, on addition of the latter to cold water and hydrochloric acid, a brown resin; these changes were not avoided by addition of the acyl halide to a cold suspension.

The 2,2,6-trimethylcyclohexanecarboxylic acid and the campholic acid derivatives were prepared in satisfactory yields by refluxing 0.12 mole of N^4-acetylsulfanilamide suspended in 100 cc. or more of dry dioxane with 0.1 mole of the appropriate acyl chloride for two hours. After the chilled mixture was poured into cold water, the product was allowed to solidify and was then purified by recrystallization from dilute alcohol or from solutions of the sodium salts to which acid was added in small successive portions. These N^4-acetyl-N^1-naphthenylsulfanilamides were insoluble in water, in 5% hydrochloric acid or in 30 or 60 parts of olive oil but were soluble (1 in 30) in 5% sodium hydroxide solution and in alcohol (except the cyclopentanecarbonyl derivative, which required more than 30 parts).

N^1-Naphthenylsulfanilamides.—Thse compounds were obtained from the corresponding N^4-acetyl derivatives by alkaline hydrolysis[1] and were insoluble in water, in 5% acid (cyclopentanecarbonylsulfanilamide was soluble in warm acid) or in 30 parts of oil, soluble in 5% alkali solution and hot alcohol (the cyclohexane derivative was soluble in cold alcohol).

TABLE I

SOME NAPHTHENYL SULFANILAMIDES: *p*-$RNHC_6H_4SO_2NHR'$

R	R'	% Yield	M. p., °C.	Nitrogen, % Calcd.	Found
CH_3CO	*a*	64	237 -238	9.03	8.97
H	*a*	60	181 -182.5	10.44	10.53
a	H	62.5	257.5-259.5	10.44	10.55
CH_3CO	*b*	46.5	232 -233	7.64	7.64
H	*b*	39	196.5-197.5	8.64	8.50
b	H	61.5	201 -203.5	8.64	8.41
CH_3CO	*c*	77	255 -260	7.64	7.74
H	*c*	51.5	219 -221	8.64	8.67
c	H	44.5	261.5-264.5	8.64	8.36

[a] Cyclopentanecarbonyl-. [b] Campholyl-. [c] 2,2,6-Trimethylcyclohexanecarbonyl-.

N^4-Naphthenylsulfanilamides.—The N^4-derivatives were prepared by heating the appropriate acid chloride with sulfanilamide either (1) suspended in toluene and pyridine[14] or (2) dissolved in anhydrous dioxane. When the latter solvent was used, 0.1 mole of the acyl chloride was added with constant agitation to 0.11 mole of sulfanilamide dissolved in 200 cc. of dioxane. The mixture was refluxed for two hours, cooled, diluted with water, and filtered, the residue being recrystallized from dilute alcohol. The N^4 derivatives were insoluble in water, 5% acid or in 30 parts of oil (two were soluble in 60 parts) but dissolved in alcohol and in 5% alkali (except the cyclohexane derivative, which did not dissolve in hot or cold alkali).

In Table I will be found the melting points, analyses, and % yields obtained for each of these compounds.

Several of these compounds were kindly tested by Parke, Davis and Company for toxicity on the mouse and for effectiveness in the treatment of some bacterial infections in the mouse. In the N^1 series, N^1-cyclopentanecarbonylsulfanilamide, with a therapeutic ratio of 25:1, was most toxic,[15] campholyl least; only cyclopentanecarbonylsulfanilamide was slightly effective in treatment of *Streptococcus hemolyticus* infections. N^4-Cyclopentanecarbonyl- and N^4-campholylsulfanilamides exhibited low toxicity and were moderately effective in *S. hemolyticus* infections and slightly effective in *S. viridans* infections. None showed activity in pneumococcic or staphylococcic infections.

Summary

1. Acylsulfanilamides have been prepared from cyclopentanecarboxylic, campholic and 2,2,6-trimethylcyclohexanecarboxylic acids and some of their properties are reported.

2. Some of these compounds were moderately or slightly effective in streptococcus infections in mice but were ineffective in pneumococcic or meningococcic infections. Low toxicity was exhibited.

(15) For N^1-cyclopentanecarbonylsulfanilamide, the ratio of L. D.-50 (dosage sufficient to kill 50% of a group of animals) to the minimal dose exerting a therapeutic effect in *Streptococcus hemolyticus* infections was 25:1.

AUSTIN, TEXAS RECEIVED SEPTEMBER 11, 1944

[CONTRIBUTION FROM THE AMMONIA DEPARTMENT OF E. I. DU PONT DE NEMOURS & CO., INC.]

The Determination of Unsubstituted Acid Amides[1]

BY J. MITCHELL, JR., AND C. E. ASHBY

Acid amides usually are identified indirectly by hydrolysis to the corresponding acids or directly by the formation of derivatives with xanthydrol,[2] phthalyl chloride,[3] oxalic acid[4] and metals, such as mercury.[5] These reactions while serving as specific methods for the identification of amides are not applicable to quantitative analysis.

Olsen[6] used a saponification technique for the quantitative determination of N-substituted amides. This analysis in addition to requiring a long refluxing step is not generally applicable to primary amides. Several methods for the determination of specific amides have been reported. Thus formamide may be determined by alkaline hydrolysis followed by permanganate oxidation of the formate ion and urea by reaction with urease, xanthydrol or ninhydrin.[7]

Numerous investigators have shown that some nitriles may be prepared by the action of acetyl or benzoyl chloride on amides[8,9] and, in specific cases, anhydrides[9,10] have been used for this purpose.

(1) Presented before the Division of Analytical and Micro Chemistry at the New York meeting of the American Chemical Society, Sept. 11, 1944.

(2) Phillips and Pitt, THIS JOURNAL, **65**, 1355 (1943).

(3) Evans and Dehn, *ibid.*, **51**, 3651 (1929).

(4) MacKenzie and Rawles, *Ind. Eng. Chem., Anal. Ed.*, **12**, 737 (1940).

(5) Williams, Rainey and Leopold, THIS JOURNAL, **64**, 1738 (1942).

(6) Olsen, *Die Chemie*, **56**, 202 (1943).

(7) Van Slyke and Hamilton, *J. Biol. Chem.*, **150**, 471 (1943). The ninhydrin ureide has been prepared in this laboratory according to Van Slyke's procedure. It was shown by titration with Karl Fischer reagent that this compound is the monohydrate.

(8) Pinner, *Ber.*, **25**, 1435 (1892).

(9) Titherley, *J. Chem. Soc.*, **79**, 411 (1901); **85**, 1673 (1904).

(10) Kremann and Wenzing, *Monatsh.*, **38**, 445 (1917).

In the present research it was found that unsubstituted amides react quantitatively with 3,5-dinitrobenzoyl chloride, in the presence of pyridine, according to the equation

$$RCONH_2 + (NO_2)_2C_6H_3COCl \longrightarrow RCN + (NO_2)_2C_6H_3COOH + HCl \quad (1)$$

The new procedure combines this reaction with a blank, finally involving the acylation of alcohol

$$CH_3OH + (NO_2)_2C_6H_3COCl \longrightarrow (NO_2)_2C_6H_3COOCH_3 + HCl \quad (2)$$

From an examination of these equations it is evident that the increase in acidity of sample over blank is equivalent to the amide originally present.

The new method is generally applicable to the quantitative analysis of the primary amides of mono- and dibasic aliphatic and aromatic acids.

Experimental

Reagents.—Approximately 2 molar 3,5-dinitrobenzoyl chloride is prepared by dissolving 461 g. of Eastman Kodak Company 3,5-dinitrobenzoyl chloride in sufficient purified anhydrous 1,4-dioxane to make 1 liter of solution. This reagent, which is initially dark brown in color, is treated with activated carbon, such as "Darco," and rapidly filtered, care being taken to protect it from excessive exposure to moisture. The final solution should be no more than light yellow in color. Other reagents include C. P. dry pyridine, dry methanol and 0.5 *N* sodium methylate in methanol, prepared directly from sodium and anhydrous alcohol.

Analytical Procedure.—The sample, containing about 10 milliequivalents of amide, is weighed into a 250-ml. glass-stoppered volumetric flask containing 15 ml. of the 3,5-dinitrobenzoyl chloride reagent and 5 ml. of pyridine. The flask, together with a blank, is placed in a water-bath at 60° for thirty minutes (70° for one hour when analyzing amides of dibasic acids[11]). At the end of this time the flasks are removed and cooled in ice. The excess acyl chloride is decomposed with dry methanol added in two increments, first 2 ml. and after five minutes an additional 25 ml. is added. The solution is titrated with 0.5 *N* sodium methylate, using phenolphthalein or ethyl bis-2,4-dinitro-phenyl acetate[12,13] as indicator. The net increase in acidity of sample over blank, after correction for free acid and water originally present in the sample, is equivalent to the primary amide.

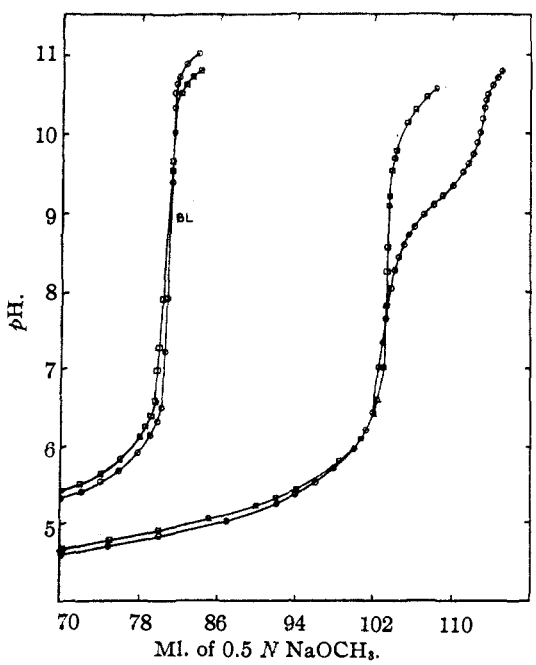

Fig. 1.—Titration curve of formamide reaction product: ○, $HCONH_2$ (10.75 mm.); □, $HCONH_2$ + HCHO.

Analytical Results.—Table I shows the results obtained on a number of unsubstituted amides. With the exception of formamide the samples were titrated to an indicator. In some cases where the reaction products were colored ethyl bis-2,4-dinitrophenyl acetate was used. In general the precision and accuracy were about ±0.3%.

TABLE I

ANALYTICAL DATA FOR PRIMARY AMIDES

Substance	Condition	Found (wt. %)
Formamide[b]	0.5 hr.—60° (1)[a]	101
Acetamide[c]	0.5 hr.—60° (6)	100.0 ± 0.2
Diacetamide hydrochloride[d]	0.5 hr.—60° (2)	100.0 ± 0.0
Propionamide[c]	0.5 hr.—60° (4)	99.5 ± 0.2
Butyramide[c]	0.5 hr.—60° (4)	99.6 ± 0.3
Isobutyramide	0.5 hr.—60° (2)	100.4 ± 0.2
n-Valeramide	0.5 hr.—60° (2)	100.4 ± 0.1
Heptamide	0.5 hr.—60° (2)	100.8 ± 0.2
Succinamide[e]	1 hr.—70° (2)	98.9 ± 0.4
Glutaramide[e]	1 hr.—70° (2)	100.3 ± 0.1
Adipamide	1 hr.—70° (6)	99.4 ± 0.2
Benzamide[c]	0.5 hr.—60° (2)	95.5 ± 0.3
Salicylamide	0.5 hr.—60° (2)	100.2 ± 0.5
p-Nitrobenzamide	0.5 hr.—65° (2)	94.4 ± 0.2
Phthalamide	1 hr.—65° (2)	95.8 ± 0.3
Furoamide	0.5 hr.—65° (2)	101.5 ± 0.2

[a] Figures in parentheses represent number of individual determinations. [b] du Pont chemical. [c] Eastman Kodak Co. recrystallized. [d] Prepared by action of hydrogen chloride on acetamide. [e] Prepared from corresponding methyl esters; all others Eastman Kodak Co. chemicals.

The titration curve of formamide, Fig. 1, indicated the presence of a weakly acidic product, which was removed by the addition of formalin solution before titration. This was shown to be hydrocyanic acid by titration to a silver electrode. In another experiment designed to identify the end products adiponitrile was isolated from the reaction of adipamide with the reagent as a fraction boiling at 150° (10 mm.). Its identity was established by hydrolysis to adipic acid and also by the preparation of the 2,4,6-trihydroxyphenyl ketone by means of the Hoesch synthesis.[14]

(11) Dibasic acid amides are insoluble in the reaction medium requiring a higher temperature, a fine state of division and frequent shaking. Four mm. glass beads, introduced into the flask, aid in dispersing the solid.

(12) Fehnel and Amstutz, *Ind. Eng. Chem., Anal. Ed.*, **16**, 53 (1944). This indicator is sold by Eastman Kodak Company and by R. P. Cargille, 118 Liberty Street, New York 6, N. Y., under the trade name "Clearol Blue."

(13) In some cases, notably formamide, the reaction products result in dark colored solutions, requiring a potentiometric titration.

(14) Howells and Little, THIS JOURNAL, **54**, 2451 (1932).

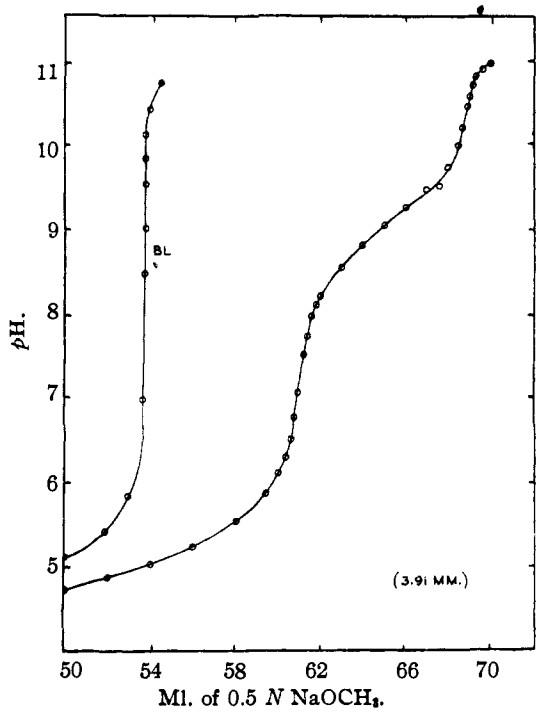

Fig. 2.—Titration curve of salicylamide reaction product.

The titration of the salicylamide reaction product to an indicator gave two moles of acid per mole of amide. However, the potentiometric curve, Fig. 2, indicated the presence of a weakly acidic constituent, presumably unreacted phenolic hydroxyl. This assumption is based on an experiment in which the excess 3,5-dinitrobenzoyl chloride when decomposed with water indicated no reaction with the hydroxyl group. In this case the net decrease in acidity would be equivalent to the extent of benzoylation, according to the reactions[15]

$$ROH + (NO_2)_2C_6H_3\cdot COCl \longrightarrow (NO_2)_2C_6H_3\cdot COOR + HCl \quad (3)$$

$$H_2O + (NO_2)_2C_6H_3\cdot COCl \longrightarrow (NO_2)_2C_6H_3\cdot COOH + HCl \quad (4)$$

Some primary amides reacted abnormally or gave acidic products. The potentiometric titrations of the urea and biuret products, Fig. 3, indicated the presence of a weakly acidic constituent. Maximum net titers were equivalent to 1.3 and 1.85 moles of acid per mole of urea and biuret, respectively. Acetyl urea, Fig. 3, gave a single inflection point, indicative of some interference. The net titer was equivalent to about 1.3 moles per mole of acetyl urea. It is surprising that allyl urea failed to react. Oxamide, apparently because of its insolubility, reacted only partially. Malonamide, although titrating to a sharp end-point, gave consistently high results averaging about 2.5 moles of acid per mole of amide. *l*-Asparagine apparently reacted normally but because of the high color of the product required a potentiometric titration. A single sharp inflection point was obtained which calculated 106.7% as this amino acid. In this experiment the commercial asparagine was used without further purification.

(15) The simultaneous quantitative reaction in which the nitrile is formed would not introduce any interference since its effect would be the same as that of the blank decomposed with water.

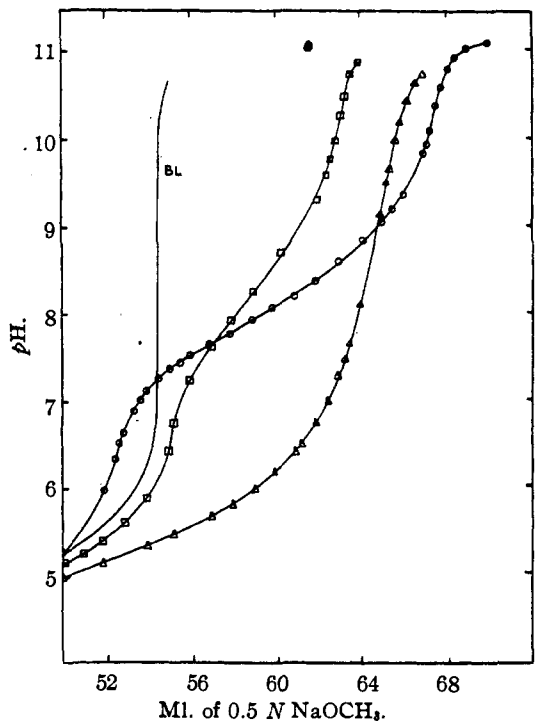

Fig. 3.—Titration curves of urea, biuret and acetylurea reaction products: ○, urea (5.37 mm.); □, biuret (2.31 mm.); Δ, acetylurea (4.67 mm.).

During the development of the new procedure other acylating agents were tried. Acetamide treated with excess acetylpyridinium chloride in purified dioxane gave values of about 108% acetylation and 16% dehydration, assuming mole for mole reaction. The acetylation data were obtained by decomposing the excess acetyl chloride with water. In this case as well as in the attempted benzoylation of salicylamide, the net decrease in acidity was equivalent to the amount of acetylation.

Benzoyl chloride and acetamide in the presence of pyridine indicated about 45% benzoylation and 60% dehydration after one hour at 70°. Titherley[9] has shown that in the absence of pyridine the dehydration reaction follows two routes

$$CH_3CONH_2 + C_6H_5COCl \longrightarrow CH_3CN + C_6H_5COOH + HCl \quad (5)$$

and to some extent

$$CH_3CONH_2 + 2C_6H_5COCl \longrightarrow CH_3CN + (C_6H_5CO)_2O + 2HCl \quad (6)$$

An experiment was devised to ascertain whether there was any evidence of anhydride formation in the presence of pyridine under conditions similar to those of the general procedure.

Fifteen ml. of 1.5 molar benzoyl chloride in dioxide and 5 ml. of pyridine were transferred to each of two 250-ml. volumetric flasks. Five ml. of a dioxane solution, containing 8.6 millimoles of acetamide, was added. The mixtures were heated together with blanks for one hour at 70°. At the end of this time the samples were cooled. Anhydrous methanol was added to both samples in two increments—first, 2 ml. and after five minutes 23 ml. To one 10 ml. of pyridine was added and the final solution titrated with 0.5 *N* aqueous sodium hydroxide. The other was titrated directly with 0.5 *N* sodium methylate in methanol.

In the first case any anhydride formed would hydrolyze to two moles of free acid, but in the anhydrous environment the anhydride would titrate mole for mole with the methylate

$$(C_6H_5CO)_2O + NaOCH_3 \longrightarrow C_6H_5COOCH_3 + C_6H_5COONa \quad (7)$$

Thus the net result would be low in proportion to the amount of anhydride formed. Results of 60 and 62%, respectively, indicated that little or no anhydride was formed under these conditions.

It is interesting to note that acetamide and 3,5-dinitrobenzoyl chloride showed no evidence of benzoylation. An experiment in which excess reagent was decomposed with water gave 0.0% reaction.

No interference was encountered from N-substituted amides, urethans and anilides. Negative results were obtained on urethan, amyl carbamate, melamine, dimethylformamide, acetanilide and propionanilide. Obviously amines or alcohols will not interfere beyond using up some of the reagent.

Interfering Substances.—Water and free acids interfere by increasing the hydrogen ion concentration of the final solution. Since both reactions are stoichiometric, however, the results can be corrected directly. Aldoximes presumably are dehydrated according to the reaction

$$RC(H)=NOH + (NO_2)_2C_6H_3COCl \longrightarrow RCN + (NO_2)_2C_6H_3COOH + HCl \quad (8)$$

An experiment in which butyraldoxime was heated at 60° for thirty minutes with the acyl chloride gave an increase in acidity equivalent to 89% dehydration.

The authors extend their thanks to L. B. Woolaver, of this laboratory, for his aid in the identification of the adipamide reaction product and in the analysis of several of the amides.

Summary

1. A new procedure for the determination of primary amides, based on quantitative reaction with 3,5-dinitrobenzoyl chloride, has been described.

2. Quantitative analytical data are presented for sixteen amides. The variable reactions of several other amides are discussed.

3. The reactions of acetamide with other acylating agents have been examined.

4. The subject of interfering substances is discussed briefly.

WILMINGTON, DELAWARE RECEIVED OCTOBER 24, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF CORNELL UNIVERSITY]

Donor-Acceptor Bonding. III. Methyl Cyanide Addition Compounds of Boron Trichloride and Boron Trifluoride

BY A. W. LAUBENGAYER AND D. S. SEARS[1]

The conditions favoring the formation of molecular addition compounds by donor–acceptor bonding and the important consequences of such bonding have been discussed in the first paper of this series.[2] The cyanide group with an unshared pair of electrons on the nitrogen has strong donor possibilities and many 1:1 addition compounds of cyanides with acceptor molecules, such as the boron halides, have been reported. Since the data available on such compounds have been very limited, the present comprehensive investigation of $CH_3CN:BCl_3$ and $CH_3CN:BF_3$ has been carried out. These systems are well suited for equilibrium studies over a considerable temperature range. $CH_3CN:BF_3$ has been described briefly by Patein[3] and by Bowlus and Nieuwland.[4]

In $CH_3CN:BCl_3$ and $CH_3CN:BF_3$, the boron atoms have tetrahedral coördination and the carbon, nitrogen and boron atoms should have a linear arrangement, giving symmetrical molecules favorable for structural studies. Because they are virtually completely dissociated in the vapor phase it has been impossible to determine their structures by electron diffraction methods, but a study of their crystal structures by X-ray diffraction methods will be undertaken.

Experimental

Preparation.—The compound $CH_3CN:BCl_3$ was prepared by allowing methyl cyanide to distill slowly *in vacuo* into liquid boron trichloride at −70°. The reaction vessel was attached to a vacuum apparatus[5] and any excess of reactant was removed by distillation. The compound was transferred in an anhydrous atmosphere to a

(1) Present address: The B. F. Goodrich Co., Akron, Ohio.

(2) Laubengayer and Finlay, THIS JOURNAL, **65**, 884 (1943).

(3) Patein, *Compt. rend.*, **113**, 84 (1891).

(4) Bowlus and Nieuwland, THIS JOURNAL, **53**, 3835 (1931).

(5) Laubengayer and Corey, *J. Phys. Chem.*, **30**, 1043 (1926).