furnished a monomethyl ether, presumably **1-hydroxy-4-methoxy-2,3-benzofluorenone**, pale yellow needles from acetic acid, m. p. 151–152°.

Anal. Calcd. for $C_{18}H_{12}O_3$: C, 78.3; H, 4.3. Found: C, 77.9; H, 4.6.

The monomethyl ether was converted into its silver salt, an orange-red insoluble substance, and a suspension of this in methanol containing excess methyl iodide was boiled for one hour. The resulting **1,4-dimethoxy-2,3-benzofluorenone** formed bright yellow needles from ethanol, m. p. 171–172°.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.6; H, 4.8. Found: C, 78.3; H, 4.6.

When the monomethyl ether was boiled for a few minutes with acetic anhydride containing potassium acetate, it yielded **1-acetoxy-4-methoxy-2,3-benzofluorenone**, bright yellow needles from acetic acid, m. p. 163–164°.

Anal. Calcd. for $C_{20}H_{14}O_4$: C, 75.4; H, 4.4. Found: C, 75.5; H, 4.6.

To show that the cyclization did not involve the hydroxyl groups of III, the dimethyl ether obtained from the cyclization product was also synthesized from ethyl 1,4-dimethoxy-3-phenyl-2-naphthoate. An excess of 10% sodium hydroxide was added dropwise to a warm alcoholic solution of 2 g. of methyl sulfate and 1 g. of III. Water and ether were then added, the ether was removed, and the resulting oil was warmed at 60° for ten minutes with 10 ml. of concd. sulfuric acid. Water was added, and the solid product was triturated with dilute sodium hydroxide. The alkali-insoluble part separated from alcohol in the form of yellow needles (0.5 g.) that melted at 171–172° alone or mixed with the dimethyl ether described above. The alkali-soluble substance, orange plates from acetic acid (*ca.* 50 mg.), m. p. 214–215°, was presumably **4-hydroxy-1-methoxy-2,3-benzofluorenone**. Its solution in aqueous alkali was blue-violet.

Anal. Calcd. for $C_{18}H_{12}O_3$: C, 78.3; H, 4.3. Found: C, 77.9, 78.3; H, 4.5, 4.7.

Summary

Contrary to a result previously claimed, the conversion of ethyl 1,3-diketo-2-phenylindene-2-acetate into ethyl 1,4-dihydroxy-3-phenylnaphthoate was not brought about by sulfuric acid. Indeed, the substituted naphthoic ester is not stable to sulfuric acid, but is converted by this reagent into 1,4-dihydroxy-2,3-benzofluorenone.

MINNEAPOLIS, MINNESOTA RECEIVED NOVEMBER 16, 1944

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

Some Naphthenyl Sulfanilamides

BY J. RICHARD STOCKTON AND H. L. LOCHTE

Although hundreds of sulfanilamide derivatives have been synthesized, relatively few alicyclic acyl derivatives have been prepared.[1] Since a number of naphthenic acids had been investigated in connection with other researches, the preparation of N^1- and N^4-acylsulfanilamides from some of these acids was undertaken. Thus from campholic acid have been prepared N^4-campholylsulfanilamide, N^4-acetyl-N^1-campholylsulfanilamide and N^1-campholylsulfanilamide. Analogous compounds were obtained from cyclopentanecarboxylic acid and from 2,2,6-trimethylcyclohexanecarboxylic acid.

Experimental

The Acids.—Cyclopentanecarboxylic acid was prepared by a series of reactions starting with adipic acid as follows. Cyclopentanone was obtained by fusion of adipic acid with barium hydroxide.[2] Hydrogenation of cyclopentanone by the method of Adkins, Homer and Cramer[3] but with Raney nickel as catalyst gave the alcohol. Cyclopentanol was converted to the chloride by treating the alcohol (1) with dry hydrogen chloride at 110°[4] or (2) with zinc chloride and concentrated hydrochloric acid[5] and most satisfactorily by (3) refluxing one mole of hydrochloric acid with 0.5 mole of cyclopentanol for six hours; the latter method gave a 59% yield. Yarnall and Wallace,[6] using a hydrochloric acid–calcium chloride method, reported a yield of 46%. Cyclopentanecarboxylic acid was prepared from the chloride by the Grignard reaction.[7,8] Since this gave a yield of only 20%, the Grignard reaction was repeated with the bromide,[9] and a yield of 87% was obtained. The superiority of the bromide for this reaction was unexpected since Gilman and Zoellner[7] found cyclohexyl chloride preferable to the bromide for making cyclohexanecarboxylic acid.

Campholic acid was prepared by the fusion of *d*-camphor with dry potassium hydroxide in a steel bomb.[10,11]

2,2,6-Trimethylcyclohexanecarboxylic acid was isolated from California petroleum and identified in this Laboratory.[12]

The acyl halides were prepared by treating the acids with about 1.3 equivalents of thionyl chloride and—after allowing effervescence to cease or after permitting the mixture to stand overnight—heating in a bath at 70 to 80° for two hours. The products were fractionated at reduced pressures.

N^4-Acetyl-N^1-naphthenylsulfanilamides.—The derivative of cyclopentanecarboxylic acid was prepared by condensation of the acyl chloride with N^4-acetylsulfanilamide[13] in dry pyridine.[1] However, the treatment of N^4-acetylsulfanilamide in dry pyridine with the acid chloride of campholic acid or of 2,2,6-trimethylcyclohexanecarboxylic acid resulted in either case in the formation of large amounts of an amorphous, brittle, tan solid (insoluble in water, acid or alkali, soluble in acetone) but only small quantities of the desired derivatives. These latter reactions were endothermic, requiring continuous heating to maintain the desired temperature of 100–110°, whereas the condensation of acyl chlorides with N^4-acetylsulfanilamide in anhydrous pyridine is typically an exothermic process. Longer periods of heating produced no observable improvement. Attempts to condense 2,2,6-trimethylcyclohexanecarbonyl chloride with N^1-potassium-N^4-acetylsulfanilamide[14] suspended in boiling pyridine[1] produced a deeply colored, vis-

(1) Crossley, Northey and Hultquist, THIS JOURNAL, **61**, 2950 (1939).

(2) "Organic Syntheses," Coll. Vol. I, p. 187.

(3) Adkins, Homer and Cramer, THIS JOURNAL, **52**, 4349 (1930).

(4) Zelinsky, *Ber.*, **41**, 2627 (1908).

(5) "Organic Syntheses," Coll. Vol. I, p. 137.

(6) Yarnall and Wallace, *J. Org. Chem.*, **4**, 284 (1939).

(7) Gilman and Zoellner, THIS JOURNAL, **53**, 1945 (1931).

(8) "Organic Syntheses," Coll. Vol. I, p. 353.

(9) "Organic Syntheses," Vol. XIX, p. 88 (1939).

(10) Williamson, Thesis, University of Texas, June, 1941.

(11) Rupe and Kloppenburg, *Helv. Chim. Acta*, **2**, 363 (1919).

(12) Shive, Horeczy, Wash and Lochte, THIS JOURNAL, **64**, 385 (1942).

(13) "Organic Syntheses," Coll. Vol. I, p. 8.

(14) Miller, Rock and Moore, THIS JOURNAL, **61**, 1198 (1939).

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).