water. After cooling to room temperature, the reaction mixture was diluted with 2 volumes of water and chilled in an ice bath. The flocculent white precipitate was removed by suction filtration and washed successively on the filter with 75 ml. portions of water, acetone, and ether; yield 142.7 mg. The entire 142.7 mg. of dihydrosphingosine-1-phosphate, 0.418 mM, were oxidized with periodic acid as previously described.[2] The consumption of periodate was 0.384 mM. This result indicates 92% completion of the reaction. The palmitaldehyde, isolated as the 2,4-dinitrophenylhydrazone, melted at 105–106°; yield 42 mg.

Acknowledgment. The author wishes to acknowledge the assistance of Mr. Wilson Woodbeck in the preparation of the beef spinal cord sphingolipides. Mrs. Florence Brand in the nitrogen determinations, Mrs Sonia Braun in the phosphorus analyses, and Miss Mary Veralli, Miss Leona Crook, Mr. James Clark, and Dr. Paula Raizman in preparing the sphingosine sulfate employed in this investigation.

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Some Observations on the Iodoform Test

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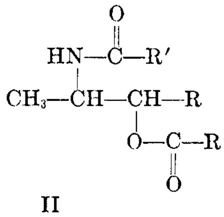
Received January 26, 1959

The reactivity of various hypohalite solutions on organic compounds and the scope of this reactivity was adequately reviewed by Fuson and Bull[3] in 1934, and since that time relatively few new structure types have been found to give a positive iodoform test (Lieben's Reaction). These new structures which gave the iodoform test could nevertheless always be explained by hydrolysis, cleavage, or oxidation. Thus α,β-unsaturated ketones not having the requisite methyl ketone or methyl carbinol grouping, could yet yield iodoform if they are capable of forming acetaldehyde or saturated methyl ketones upon a reverse aldol condensation.[4] Upon treatment with sodium hypoiodite 5-methyl-2-furoic acid also yielded iodoform.[5]



II

IIa. R = CH_2OCH_3; R′, R″ = CH_3

IIb. R, R′, R″ = C_2H_5

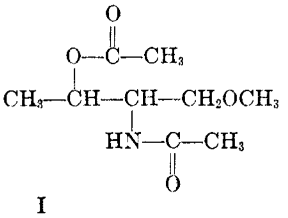
IIc. R, R′, R″ = CH_3

In the course of an investigation on the structure of Elaiomycin,[6] the iodoform test was used in an attempt to distinguish between two possible structures of a degradation product, *N*-(2-hydroxy-1-methylenemethoxypropyl)acetamide, acetate ester (I) and *N*-(2-hydroxy-3-methoxy-1-methylpropyl)-acetamide, acetate ester (IIa).

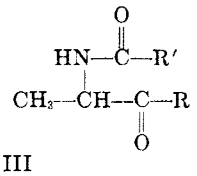
Distinction between these two structures by the iodoform test was discovered impossible when synthetic IIa yielded iodoform.

While systems which contain the group CH_3-$CHNH_2$— are known to give a positive test,[3] the conditions of the iodoform test employed in this work were not vigorous enough to hydrolyze an acylated amine. Alanine and isopropylamine which gave a positive test were acetylated to *N*-acetylalanine and *N*-isopropylacetamide, respectively, and the iodoform test failed.

That the esterified methyl carbinol system was hydrolyzed under the standard conditions to give the requisite grouping for iodoform formation was demonstrated by positive tests on *O*-acetyl lactic acid and *N*-(2-hydroxy-1-methylpropyl)acetamide, acetate ester (IIc).



I



III

IIIa. R = CH_2OCH_3; R′ = CH_3
IIIb. R, R′ = C_2H_5

Treatment of *N*-(3-methoxy-1-methylacetonyl)-acetamide (IIIa) with sodium hypoiodite also resulted in the formation of iodoform. The ketone IIIa would be formed in the hydrolysis and oxidation of IIa with sodium hypoiodite. Further, *N*-(1-

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(2) Present address: Department of Chemistry, Duquesne University, Pittsburgh, Pa.

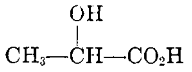
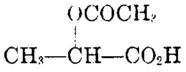
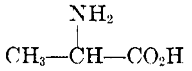
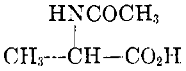
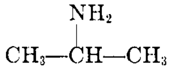
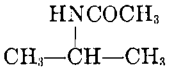
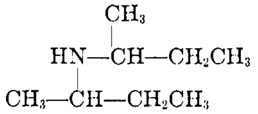
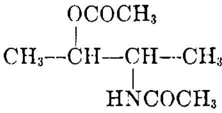
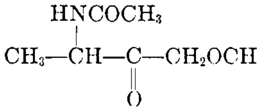
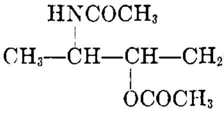
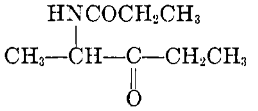
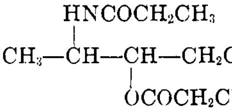
(3) R. C. Fuson and B. A. Bull, *Chem. Revs.*, **15**, 275 (1934).

(4) V. I. Esafov and N. M. Stafeeva, *Zhur. Anal. Khim.*, 6, 195 (1951); *Chem. Abstr.*, **45**, 8404 (1951).

(5) K. Maekawa, *J. Fac. Agr. Kyushu Univ.*, **9**, 149 1949); *Chem. Abstr.*, **48**, 2029 (1954).

(6) C. L. Stevens, B. T. Gillis, J. C. French, and T. H. Haskell, *J. Am. Chem. Soc.*, **80**, 6088 (1958).

Compounds Tested[7]

		Iodoform			Iodoform
1.	 $CH_3-CH(OH)-CO_2H$	(+)	7.	 $CH_3-CH(OCOCH_3)-CO_2H$	(+)
2.	 $CH_3-CH(NH_2)-CO_2H$	(+)	8.	 $CH_3-CH(HNCOCH_3)-CO_2H$	(−)
3.	 $CH_3-CH(NH_2)-CH_3$	(+)	9.	 $CH_3-CH(HNCOCH_3)-CH_3$	(−)
4.	 $CH_3-CH(HN-CH(CH_3)-CH_2CH_3)-CH_2CH_3$	(+)	10.	 $CH_3-CH(OCOCH_3)-CH(HNCOCH_3)-CH_3$ (IIc)	(+)
5.	 $CH_3-CH(HNCOCH_3)-C(=O)-CH_2OCH_3$ (IIIa)	(+)	11.	 $CH_3-CH(HNCOCH_3)-CH(OCOCH_3)-CH_2OCH_3$ (IIa)	(+)
6.	 $CH_3-CH(HNCOCH_2CH_3)-C(=O)-CH_2CH_3$ (IIIb)	(+)	12.	 $CH_3-CH(HNCOCH_2CH_3)-CH(OCOCH_2CH_3)-CH_2CH_3$ (IIb)	(+)

methylbutan-2-onyl)propionamide (IIIb) and *N*-(2-hydroxy-1-methylbutyl)propionamide, propionate ester (IIb) with a similar structural arrangement also gave positive iodoform tests.

Thus, compounds with the general structure III or those compounds which can produce this structural grouping under the conditions of the iodoform test represent a new structure type capable of positive results in the iodoform test.

The observed reaction is postulated to occur by oxidation of III in the α-position. Subsequent decomposition can then occur leading to a reactive methyl ketone.

EXPERIMENTAL[8]

Iodoform tests. All iodoform tests were performed according to the procedure of McElvain[7] using 7 drops of sample, 2.5 ml. of water, 5 ml. of 5% sodium hydroxide solution, and the required amount of iodine-potassium iodide solution necessary to give an iodine color. The iodoform obtained was identified by melting point and mixture melting point determinations. Samples 1, 2, 3, and 4 were available compounds of reagent grade.

O-Acetyl lactic acid. Lactic acid was acetylated according to the procedure of Filachione[9] and a 67% yield of *O*-acetyl lactic acid, b.p. 85–88° (0.8 mm.), n_D^{25} 1.4230, d^{25} 1.4320, d^{25} 1.175 was obtained.

*N-Acetyl-*DL*-alanine.* DL-Alanine was acetylated with acetic anhydride by the method described in *Organic Syntheses* for glycine.[10] The *N*-acetyl-DL-alanine prepared melted 136–137°.[11]

N-Isopropylacetamide. Low temperature acylation of isopropylamine with excess acetic anhydride followed by distillation resulted in a quantitative yield of *N*-isopropylacetamide, b.p. 201–203°, n_D^{25} 1.4273, d^{25} 0.912.

N-(2-Hydroxy-1-methylpropyl)acetamide, acetate ester (IIc). Hydrogenation of 3-acetamido-2-butanone[12] (11.5 g., 0.088 mole) with platinum oxide in ethanol yielded 10 g. (87%) of *N*-(2-hydroxy-1-methylpropyl)acetamide, b.p. 112–115° (0.3 mm.), n_D^{25} 1.4664. Ten g. of this alcohol was treated with cold acetic anhydride and then warmed gently for 8 hr. Volatile material was removed under reduced pressure and on distillation there was obtained 10 g. (76%) of IIc,[13] b.p. 50° (5–8 μ), n_D^{25} 1.4526, d^{25} 1.055.

N-(3-Methoxy-1-methylacetonyl)acetamide (IIIa). Methoxyacetic anhydride, b.p. 74–77° (2 mm.), n_D^{25} 1.4259 was prepared from methoxyacetic acid, thionyl chloride, and pyridine at −15°.[14] In a 100-ml. flask equipped with condenser was placed 23 g. (0.1418 mole) of methoxyacetic anhydride, 11.3 g. (0.1418 mole) of pyridine, and 6.55 g. (0.05 mole) of *N*-acetylalanine. The reaction mixture was heated several hours on the steam bath. The mixture was then distilled to yield 3.84 g. (48%) of IIIa, b.p. 48° (5 μ), n_D^{25} 1.4562, d^{25} 1.126.

Anal. Calcd. for $C_7H_{13}NO_3$: C, 52.81; H, 8.23. Found: C, 53.23, H, 7.88.

N-(2-Hydroxy-3-methoxy-1-methylpropyl)acetamide, acetate ester (IIa). Two g. (0.0125 mole) of IIIa was reduced in absolute ethanol with 0.3 g. of prereduced platinum oxide and 0.85 equivalent of hydrogen was absorbed. Filtration of the mixture and removal of the ethanol from the filtrate under reduced pressure left a residue which was treated with excess acetic anhydride. Subsequent removal of the excess acetic anhydride and acetic acid after heating and distillation yielded 1.90 g. (75%) of IIa, b.p. 60° (0.3 μ), n_D^{25} 1.4502, d^{25} 1.109. The infrared spectrum of this compound was in agreement with the assigned structure.

Anal. Calcd. for $C_9H_{17}NO_4$: C, 53.18; H, 8.43. Found: C, 52.98; H, 8.11.

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(7) The procedure in S. M. McElvain, *The Characterization of Organic Compounds*, The MacMillan Co., New York, 1949, pp. 137, was utilized.

(8) Melting points and boiling points are uncorrected.

(9) E. M. Filachione, *Ind. Eng. Chem.*, **36**, 472 (1944).

(10) A. H. Blatt, *Org. Syntheses*, **Coll. Vol. 2**, 11, 1943.

(11) W. Shive and G. W. Shive, *J. Am. Chem. Soc.*, **68**, 117 (1946).

(12) C. C. Price, *Org. Syntheses*, **33**, 1 (1953).

(13) F. H. Dickey, W. Fickett, and H. J. Lucas, *J. Am. Chem. Soc.*, **74**, 944 (1952) report the DL-*threo*-, *erythro*-, D(+)*threo*- and L(−)*erythro*- forms.

(14) W. Gerrard and A. M. Thrush, *J. Chem. Soc.*, 741 (1952).

N-(1-Methylbutan-2-onyl)propionamide (IIIb). The procedure for the preparation of 3-acetamido-2-butanone[12] was utilized. Treatment of 20 g. (0.224 mole) of DL-alanine with 95 g. (1.2 moles) of pyridine and 174.8 g. (1.344 moles) of propionic anhydride yielded 20.2 g. (58.5%) of IIIb, b.p. 79–81° (0.1 mm.), n_D^{25} 1.4547, d^{25} 1.016.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.11; H, 9.61. Found: C, 61.30; H, 9.48.

N-(2-Hydroxy-1-methylbutyl)propionamide, propionate ester (IIb). To 4 g. (0.0254 mole) of IIIb in methanol was added slowly with swirling 750 mg. of sodium borohydride. The reaction mixture was allowed to stand overnight. Ammonium hydroxide was added to the solution. The solution was extracted with ether and the ether extracts dried over anhydrous sodium sulfate, filtered, and evaporated to leave a white solid. Recrystallization of the solid from petroleum ether–acetone yielded 2.663 g. (66%) of *N*-(2-hydroxy-1-methylbutyl)-propionamide, m.p. 113–114°. A solution of 2.563 g. of this alcohol in pyridine was added to an excess of propionyl chloride in pyridine and the mixture was allowed to stand overnight, then poured onto cracked ice. The aqueous mixture was extracted with ether and the ether extract was washed successively with dilute hydrochloric acid, water, sodium bicarbonate, and water. The ether solution was dried and then distilled to yield 1.752 g. (51%) of IIb, b.p. 101–103° (0.1 mm.), n_D^{25} 1.4523, d^{25} 1.004. The infrared spectrum of this compound was in agreement with the assigned structure.

Anal. Calcd. for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.83; N, 6.51. Found: C, 61.12; H, 9.80; N, 6.45.

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Derivatives of Sulfenic Acids.
XXIV. Synthesis of Certain Thiophenols by Cleavage of Unsymmetrical Disulfides[1]

NORMAN KHARASCH AND ALAN JAMES PARKER[2]

Received January 28, 1959

In a preceding paper of this series[3] a new synthesis of thiophenols was recorded, involving alkaline cleavage of aryl 2,4-dinitrophenol sulfides:

$$(NO_2)_2C_6H_3SAr + OCH_3^- \longrightarrow ArS^- + (NO_2)_2C_6H_3{-}OCH_3 \quad (1)$$

We now wish to describe another new method for preparing certain thiophenols, which was an outgrowth of our interests in the mechanisms of scission of the sulfur-sulfur bond.

It is well known[4] that many disulfides are cleaved by nucleophilic reagents such as CN^-, RS^-, SO_3^{--}, $(C_6H_5)_3P$, AsH_5, $S_2O_3^{--}$, *etc.* These reactions are simply nucleophilic displacements from bivalent sulfur, of a mercaptide ion, by a base with more affinity for sulfur. The reactions involve equilibria, which may be represented as in (2), where B^- is a base such as those above, and R and R′ are any groups (not necessarily different), which form a covalent bond with sulfur which is less susceptible to cleavage than the =S—S—bond.

$$R{-}S{-}S{-}R' + B^- \rightleftharpoons RS^- + R'S{-}B \quad (2)$$

In many cases, equilibrium *b* lies well to the left because of the high affinity of RS^- for sulfur, and, in other cases, the alternate scission (3) may compete with (2). If, however, B^- is a strong

$$R{-}S{-}S{-}R' + B^- \rightleftharpoons RS{-}B + R'S^- \quad (3)$$

displacing anion, and R is a strong electron withdrawing group (such as 2,4-dinitrophenyl or 2-nitro-4-chlororophenyl), the reactivity of RS^- in reaction (2) will be less than that of B^- and this will cause equilibrium (*b*) to lie to the right. Also, if R is considerably more electron withdrawing than R′, RS^- will be the more easily displaced mercaptide group, so that primarily reaction (2) and not (3), will occur. With these conditions in mind, reaction (2) can be adapted to a convenient synthesis of certain thiophenols, RSH, starting with sulfenyl chlorides, RSCl, in which R is a strong electronegative group, and choosing a less electronegative group, R′, so that R′SB, or its decomposition products, are readily soluble in water, or are volatile.

We selected 2-mercaptosuccinic acid (thiomalic acid) as the source for the group R′S, and hydroxide ion as the nucleophilic reagent for general use; ethyl mercaptan, mercaptoacetic acid, and β-mercaptoethanol are equally effective sources of the R′S group. It is also known[4] that cyanide ion and triphenylphosphine are much more powerful displacing nucleophiles for reaction (1) than is hydroxide ion, and—although less convenient—should be chosen when cleaving disulfides (RSSR′) in which R is not as strongly electron withdrawing as it is in the case of 2,4-dinitrophenyl or 2-nitro-4-chlorophenyl. In one reaction (R = 2-nitrophenyl), the use of cyanide ion as the displacing anion increased the yield of 2-nitrothiophenol by 35% over that obtained with hydroxide ion as nucleophile.

The reactions are easy to perform and lead to the desired thiophenols quickly. The sulfenyl chloride is converted almost quantitatively to the thiomalic acid derivative (Equation 4), which is a stable, odorless, crystalline disulfide. Like the aryl 2,4-dinitrophenyl sulfides of Equation (1), these disulfides cleaved rapidly to yield the thiophenol.

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[2] Australian Commonwealth Scientific and Industrial Research Organization post-doctoral fellow at the University of Southern California, 1958–1959.

[3] N. Kharasch and R. Swidler, *J. Org. Chem.*, **19**, 1704 (1954).

[4] *Cf.* the reviews by O. Foss in *Organic Sulfur Compounds*, edited by N. Kharasch, Vol. 1, Pergamon Press, 1959; and A. J. Parker and N. Kharasch, *Chem. Revs.*, in press.