TABLE IV

RATES OF REACTION WITH BENZALDEHYDES[a]

	$k \times 10^3$ L. Mole^{-1} Sec.$^{-1}$		
		*p*H 8.5	*p*H 6.0
	25.0°	64.0°	25.0°
Benzaldehyde	7.68	69.1	11.1
p-Anisaldehyde	2.30	14.5	16.1
p-Nitrobenzaldehyde	25.4	—	4.11

[a] In 60% aqueous ethanol.

Although the reactions at 25° proceeded to 100% completion, at 64.0° both cyclohexanone and cyclopentanone only reacted to 70–75% with a slight excess of Girard-T. This shows that the overall reaction is exothermic and suggests that it may be more convenient to prepare Girard derivatives by reaction at room temperature for a longer time.

The rates of reaction of benzaldehyde, *p*-anisaldehyde and *p*-nitrobenzaldehyde were similarly determined at 25° and at *p*H 6.0 and 8.5 (Table IV). Benzaldehyde and *p*-anisaldehyde showed increases of 9 and 6.5 times, respectively, on raising the temperature to 64° at *p*H 8.5, corresponding to energies of activation of 11.2 and 9.4 kcal/mole, respectively. In alkaline solution at 25° *p*-nitrobenzaldehyde reacted 3.3 times as fast as benzaldehyde, whereas *p*-anisaldehyde reacted at about $^1/_3$ the rate, while in acid solution *p*-anisaldehyde reacted 1.5 times as fast as benzaldehyde and *p*-nitrobenzaldehyde at about $^1/_3$ the rate.

Aqueous ethanol was not a suitable solvent for studying the reaction with high molecular weight ketones due to their low solubility. However 90%-isopropyl alcohol-water was found to dissolve sufficient inorganic salts to prepare buffered solutions. Steroid ketones were also reasonably soluble in this solvent and the rate of reaction of 3-cholestanone with Girard-T reagent at 25° and at various *p*H (buffers, chloride *p*H 2.0, 3.5, acetate *p*H 4.5, 5.5 and phosphate pH 8.5) has been determined (Table V).

TABLE V

RATES OF REACTION OF 3-CHOLESTANONE[a]

*p*H	$k \times 10^3$ L. Mole-1 Sec.$^{-1}$
2.0	4.2
3.5	1020
4.5	960
5.5	5.9
8.5	0.74

[a] In 90% isopropyl alcohol-water at 25.0°.

The reaction was extremely slow in alkaline-medium, but very rapid at *p*H 3.5. The rate, however, decreased again at higher acidity since the reaction is reversible and the hydrolysis of the Girard derivative is catalyzed by strong acids.[6]

(6) O. H. Wheeler and O. Rosado, forthcoming publication.

The first 80% or so of the reaction with 3-cholestanone followed second order kinetics, but steroid ketones were found to react with more than one equivalent of Girard-T reagent in isopropyl alcohol. The nature of this reaction and other aspects of reactions with steroid ketones will be discussed in a forthcoming publication.

EXPERIMENTAL

Titration of Girard-T reagent. Girard-T reagent (Arapohoe Chemicals) was recrystallized twice from ethanol and stored in a desiccator.

Various aqueous buffer solutions were prepared of total concentration 0.2*M* from A.R. salts. The phosphate buffer (*p*H7) used for the titrations was 0.62*M* disodium hydrogen hydrogen phosphate and 1*M* sodium hydrogen phosphate. Blank titrations of these buffers and the titration and the Girard-P are given in Tables I and II.

Kinetic measurements. The freshly distilled or recrystallized aldehyde or ketone (*ca.* 0.5 mM) was dissolved in absolute ethanol (10 ml.) (isopropyl alcohol in the case of 3-cholestanone), aqueous phosphate buffer *p*H7 (20 ml.) added and the solution allowed to attain thermal equilibrium in a constant temperature bath at 25° (or a boiling methanol bath at 64°), and 0.0125*M* Girard-T reagent in absolute ethanol (20 ml.) at the same temperature added. The resultant solution had an apparent *pH* of 8.5 (glass electrode). Aliquots (5 ml.) were withdrawn at intervals added to 0.05*N* iodine solution (5 ml.) in phosphate buffer *p*H7 (10 ml.), and the excess iodine titrated with 0.05*N* sodium thiosulfate using starch as indicator.

Acknowledgment. The authors are grateful to the National Research Council of Canada and Syntex of Mexico City for financial assistance and to Syntex and Arapohoe Chemicals for gifts of steroids and Girard reagents, respectively.

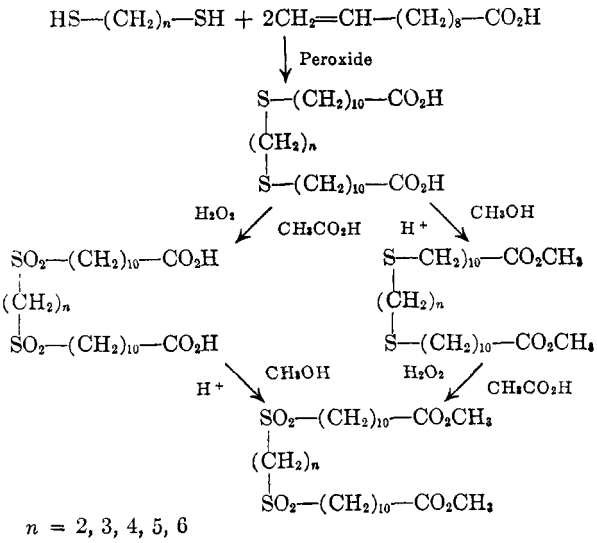
DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PUERTO RICO AND DALHOUSE UNIVERSITY
HALIFAX, N.S., CANADA

Synthesis of Some Sulfur-Containing Acids and Their Derivatives. I. Derivatives of 10-Undecenoic Acid

GEORGE S. SASIN, FREDERICK R. LONGO, RICHARD BERGER, WILLIAM DESANTIS, AND RICHARD SASIN

Received November 3, 1960

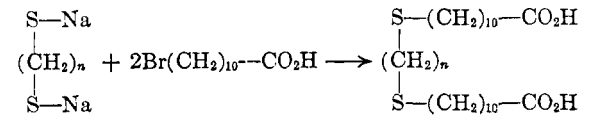
This paper reports the synthesis and reactions of some alkane bis(11-mercaptoundecanoic) acids. The alkane bis(11-mercaptoundecanoic) acids were prepared by the addition of alkane dithiols to 10-undecenoic acid under free radical conditions. The acids were esterified by methanol and oxidized to the corresponding disulfones by hydrogen peroxide in the presence of glacial acetic acid. The alkane bis(11-mercaptoundecanoic) acids were oxidized to the corresponding disulfone acids by hydrogen peroxide, and these compounds were then esterified by methanol.



n = 2, 3, 4, 5, 6

The addition of mercaptans to olefins under free radical conditions, to yield products of anti-Markownikow configuration, has been reported previously in the literature.[1-4] The addition of mercaptans to 10-undecenoic acid under free radical conditions, was reported by Koenig and Swern to yield products of anti-Markownikow configuration.[5]

The addition of alkane dithiols to 10-undecenoic acid, under free radical conditions, yielded products of anti-Markownikow configuration. This was confirmed by determining mixed melting points with authentic samples of alkane bis(11-mercaptoundecanoic) acids. The authentic samples of these compounds were prepared by treating 11-bromoundecanoic acid with the sodium salt of the appropriate alkane dithiol. A mixture of the two compounds showed no depression of the melting point.



n = 2, 3, 4, 5, 6.

The properties, yields obtained and analyses of the compounds synthesized are summarized in Table I.

The bissulfide acids and the bissulfide and bissulfone esters are white crystalline compounds of definite melting point. These compounds, as many other homologous series, show an alternation in melting points. Figure 1.[6]

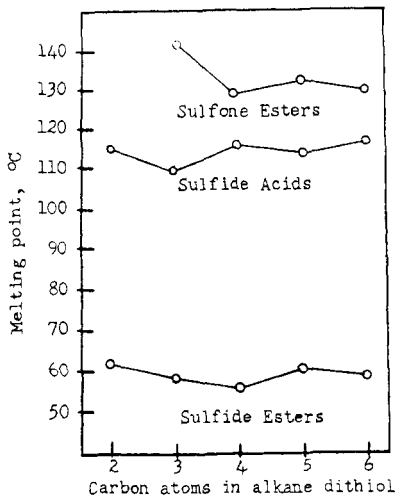


Figure 1

The bissulfone acids were found to melt with decomposition. The approximate temperature at which these compounds decompose are listed in Table I. The bissulfone acids were esterified by methanol with much greater difficulty than the bissulfide acids. The former compounds required a very large excess of methanol (125 ml. of alcohol per gram of sulfone acid) and a reflux time of twenty four hours. Using this procedure, the ethane derivative yielded only unchanged reactants. Even when the reflux time was extended to seventy-two hours, no esterification of this compound could be effected.

Traces of unchanged acids were removed from the crude bissulfide methyl esters by chromatography on Florisil.

The bissulfide acids and their methyl esters are sparingly soluble in the common organic solvents. The bissulfone acids and their methyl esters are even less soluble in the common organic solvents.

EXPERIMENTAL

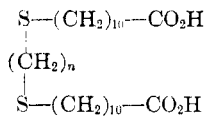
Alkane bis(11-mercaptoundecanoic) acids. To 0.054 mole of 10-undecenoic acid in a 50-ml. round-bottomed flask, fitted with a reflux condenser, was added 0.027 mole of the appropriate dithiol and the mixture was boiled under gentle reflux for 2 hr. At the end of this time, 30 ml. of carbon tetrachloride was added and the mixture was boiled under reflux for an additional 4 hr. The solid which separated on cooling was crystallized from carbon tetrachloride until successive crystallizations showed no increase in melting point. In all cases, at least four crystallizations were necessary. For the crystallizations, 12 ml. of carbon tetrachloride per gram of product were used.

Esterification of alkane bis(11-mercaptoundecanoic) acids. To 0.004 mole of the appropriate alkane bis(11-mercaptoundecanoic) acid was added 20 ml. of methanol and 0.2 g. of benzene sulfonic acid and the mixture was boiled under

(1) M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, **13**, 97 (1948).
(2) M. S. Kharasch, W. Nudenberg, and F. Kawahara, *J. Org. Chem.*, **20**, 1550 (1955).
(3) M. S. Kharasch, W. Nudenberg, and G. J. Mantell, *J. Org. Chem.*, **16**, 524 (1951).
(4) A. Fontijn and J. W. T. Spinks, *Can. J. Chem.*, **35**, 1384 (1957).
(5) N. E. Koenig and D. Swern, *J. Am. Chem. Soc.*, **79**, 4235 (1957).
(6) G. S. Sasin, F. R. Longo, O. T. Chortyk, P. A. Gwinner, and R. Sasin, *J. Org. Chem.*, **24**, 2022 (1959).

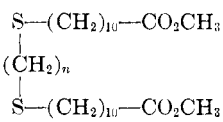
TABLE I

ALKANE BIS(11-MERCAPTOUNDECANOIC) ACIDS



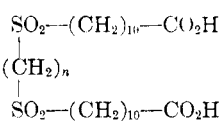
n	Yield, %	M.P.	Carbon		Hydrogen		Sulfur	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
2	60	113–114	62.1	61.8	10.0	9.9	13.8	13.6
3	47	99–100	63.1	62.5	10.2	10.0	13.5	13.8
4	40	105–106	63.7	63.7	10.3	10.3	13.1	13.0
5	41	104–105	64.2	64.5	10.4	10.6	12.7	13.1
6	51	106–107	64.9	64.5	10.4	10.4	12.3	11.8

METHYL ESTERS



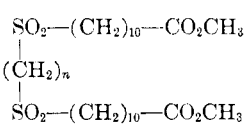
2	63	62–62.5	63.5	63.1	10.3	10.0	13.0	12.8
3	79	59.5–60	64.2	63.9	10.4	10.2	12.7	13.1
4	72	57–57.5	64.9	65.1	10.5	10.5	12.4	12.4
5	53	62.5–63	65.4	65.4	10.6	10.7	12.0	11.6
6	65	61–61.5	65.9	65.6	10.7	10.5	11.7	11.4

SULFONE ACIDS



2	96	155 dec.	54.9	55.5	8.8	8.9	12.2	12.5
3	91	166 dec.	55.6	55.7	8.9	9.1	11.8	11.5
4	95	132 dec.	56.4	56.7	9.1	9.2	11.5	11.7
5	71	164 dec.	57.0	57.4	9.2	9.3	11.2	11.1
6	96	155 dec.	57.7	57.5	9.4	9.4	11.0	10.7

SULFONE ESTERS



3	93	141–142	57.1	57.8	9.2	9.3	11.2	11.4
4	90	127–128	57.8	58.3	9.4	9.5	11.0	10.8
5	82	132–133	58.4	58.5	9.5	9.5	10.7	10.8
6	80	128–129	59.1	59.6	9.6	9.7	10.5	10.3

reflux for 6 hr. The solid which formed on cooling was separated by filtration and crystallized from methanol. The methyl esters were then chromatographed with Florisil and eluted with benzene. After removal of the benzene by distillation, the esters were crystallized once from methanol.

Oxidation of alkane bis(11-mercaptoundecanoic) acids. To 0.011 mole of the sulfide acid in a 125-ml. Erlenmeyer flask was added 25 ml. of glacial acetic acid and the flask was chilled in an ice bath. To the flask was added 0.26 mole of 30% hydrogen peroxide and the mixture was allowed to stand in the melting ice bath for 72 hr. The resulting solid was then crystallized from dioxane until successive crystallizations showed no increase in melting point. In all cases, at least three crystallizations were necessary.

Preparation of the bissulfone esters. To 0.004 mole of the sulfone acid in a 500-ml round-bottomed flask, fitted with a reflux condenser, were added 250 ml. of methanol and 0.2 g. of benzene sulfonic acid and the mixture was heated under reflux for 24 hr. The solid, which separated on cooling, was separated by filtration and washed thoroughly with water to remove all of the benzene sulfonic acid. The product was then crystallized from dioxane (15 ml. of dioxane per g. of sulfone ester) until successive crystallizations showed no increase in the melting point.

Alternate preparation of the alkane bis(11-mercaptoundecanoic) acids. To 0.06 mole of the alkane dithiol in a 500-ml. round-bottomed flask, fitted with a reflux condenser and a calcium chloride drying tube, were added 300 ml. of dry dioxane and 2.3 g. (0.1 g.-atom) of sodium metal. The mixture was heated under gentle reflux for 72 hr. or until all of the sodium had been consumed. To the resulting suspension was added 0.05 mole of 11-bromoundecanoic acid and

this mixture was heated under gentle reflux for 72 hr. The mixture was then poured into 300 ml. of water and acidified with dilute hydrochloric acid solution. The solid which formed was separated by filtration and washed with three 50-ml. portions of water. The product was then crystallized from carbon tetrachloride until successive crystallization showed no increase in the melting point.

Alternate preparation of the bissulfone esters by the oxidation of the corresponding bissulfide ester. To 0.004 mole of the chromatographed bissulfide ester in a 50-ml. Erlenmeyer flask was added 10 ml. of glacial acetic acid and the flask was chilled in an ice bath. To the flask was added 0.09 mole of 30% hydrogen peroxide and the mixture was allowed to stand in the melting ice bath for 72 hr. The resulting solid was then crystallized from dioxane until successive crystallizations showed no increase in the melting point.

DEPARTMENT OF CHEMISTRY
DREXEL INSTITUTE OF TECHNOLOGY
PHILADELPHIA 4, PA.

4,5-Dihalo and 3-Amino Analogs of Pyridoxine. New Route to 4-Deoxypyridoxine[1,2]

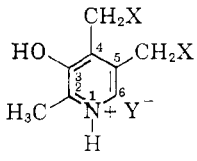
G. E. MCCASLAND, L. KENNETH GOTTWALD AND, ARTHUR FURST

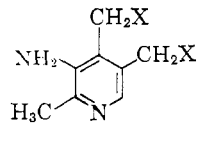
Received November 17, 1960

The anti-tumor action of nitrogen mustards has in part been attributed to their alkylating properties. Since pyridoxine (I) is involved in many physiological processes, it was of interest to synthesize an alkylating agent having a pyridoxine-like structure. An example would be the dibromomethyl hydrobromide (II), which because of its benzyl halide type structure would be expected to show good alkylating activity at least in neutral or basic solution. This compound had previously been prepared from the 3- or 4-alkyl ethers of pyridoxine by Harris and Folkers[3a] and Kuhn and Wendt.[3b] It presumably was also prepared from pyridoxine itself by Kreisky,[3c] but the first explicit description of the latter procedure is that now given.

The next compound investigated was the diiodide hydriodide (III). This product could not be obtained by treating the dibromide hydrobromide with sodium iodide in dry acetone. The dibromide free base was considered preferable for the sodium iodide reaction, but attempts to prepare the free base, even under the mildest conditions, led to a high-melting red-brown solid, which appears to be a polymeric quaternary salt[4] (V). It was then found that the diiodide hydriodide can be obtained by merely heating pyridoxine hydrochloride with concentrated hydriodic acid for a brief period; on cooling, pure III separates almost at once in the form of yellow crystals.

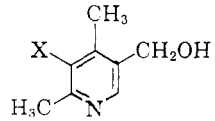
The corresponding dichloride hydrochloride[5] (IV) had previously been prepared,[6] by a sealed tube reaction of a pyridoxine alkyl ether with concentrated hydrochloric acid. We now find that IV is more conveniently prepared by reaction of pyridoxine itself with thionyl chloride.



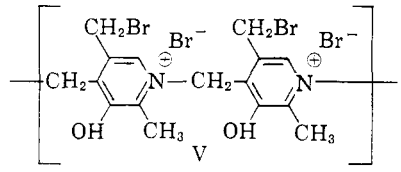


(I), X = OH, Y = Cl
(II), X = Y = Br
(III), X = Y = I
(IV), X = Y = Cl

(VI), X = OH (·HCl)
(VII), X = Br (·HBr)
(VIII), X = OAc (*N*-Ac)
(IX), X = OH (*N*-Ac)



(X), X = OH (·HCl)
(XI), X = NH_2 (·HI)



V

Some derivatives of 3-amino-3-deoxypyridoxine[7,8] (VI) were next examined. The 3-amino hydrochloride reacted with hydrobromic acid in much the same way as pyridoxine hydrochloride (see above),

(1) Paper VI on pyridoxine analogs. For preceding (unnumbered) papers, see G. E. McCasland, E. Blanz, Jr., and A. Furst, *J. Org. Chem.*, **24**, 1000 (1959) and references there cited. Taken in part from the M.S. thesis of L. Kenneth Gottwald, Graduate School, the University of San Francisco, 1961.

(2) This work was aided by Grant CY-2798 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. Gifts of pyridoxine from Drs. Karl Folkers, Merck, Sharp & Dohme Co., and Walter Gakenheimer, The Stuart Co., are gratefully acknowledged.

(3) (a) S. Harris and K. Folkers, *J. Am. Chem. Soc.*, **61**, 1247 (1939); (b) R. Kuhn and G. Wendt, *Ber.*, **72**, 311 (1939); (c) Selma Kreisky, *Monats.*, **89**, 685 (1958).

(4) Compare the polymerization of 4-bromopyridine, H. S. Mosher, p. 516 in R. C. Elderfield (editor), *Heterocyclic Compounds*, Wiley, New York, Vol. I, 1950.

(5) It was hoped that this dihalo hydrohalide series could be completed by preparing a difluoride hydrofluoride. However, all attempts to prepare the fluorine analog were unsuccessful, and there is reason to believe that such a product if prepared, would be unstable.

(6) S. Harris and K. Folkers, *J. Am. Chem. Soc.*, **61**, 3307 (1939).

(7) (a) R. K. Blackwood, *et al.*, *J. Am. Chem. Soc.*, **80**, 6244 (1958); (b) R. G. Jones and E. Kornfeld, *J. Am. Chem. Soc.*, **73**, 107 (1951).

(8) The *mono*hydrochloride of 2-methyl-3-amino-4,5-di(hydroxymethyl)pyridine was obtained by Blackwood, *et al.* (*loc. cit.*) under conditions (excess hydrogen chloride) which one might think would give a dihydrochloride. They reported a m.p. of 197–199° and a correct analysis for the monohydrochloride. Jones and Kornfeld (*loc. cit.*) reported the free base (m.p. 141.5–152°, correct analysis) and a dihydrochloride (m.p. 176–177°), but gave no analysis or preparation details for the latter.