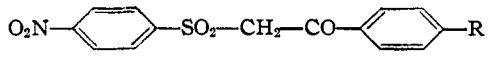
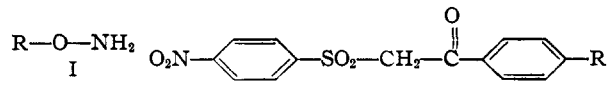
TABLE I



R	M.p., °C.	Yield, %	Solvent recryst.	Crystals	Formula	Nitrogen, % Calcd.	Found
Br[a]	173	80	Ethanol	Powder	$C_{15}H_{13}BrN_4O_2S_2$	13.18	12.92
Br	221-222	75	Ethanol	Flakes	$C_{15}H_{13}BrN_4O_4S_2$	12.25	12.42
Cl	202	91	Ethanol-acetone	Needles	$C_{15}H_{13}ClN_4O_4S_2$	13.57	13.53
CH_3	197	71	*n*-Butanol	Needles	$C_{16}H_{16}N_4O_4S_2$	14.32	14.30
(*b*)	198 (dec.)	62	Ethanol	Needles	$C_9H_{11}N_3O_2S_2$	16.34	16.37

[a] This compound was the sulfide corresponding to the formula above. [b] β-(2-Thenoyl)-propionic acid thiosemicarbazone.

derivatives of hydroxylamine (I) and thiosemicarbazones of α-(4-nitrophenylsulfonyl)-acetophenones (II).



I
R = alkyl, etc.

II
R = CH_3, Cl, Br

Although compounds of type (I) have been reported, no report of antitubercular testing or activity has been noted. However, certain hydroxamic acids have been reported to possess antituberculous properties.[1,2] Gardner and co-workers,[3] however, report that compounds of this type have little value as antitubercular agents.

The continued interest in thiosemicarbazones as possible antitubercular agents[4,5] prompted us to attempt the preparation of thiosemicarbazones (II) of a number of α-(4-nitrophenylsulfonyl)-acetophenones and of some of the corresponding amines and sulfides.[6]

None of the amines which correspond to II could be prepared by any variation of the general procedure of preparation. Although a reaction was observed and a product isolated with each of the amines, the product could not be purified sufficiently for correct analysis.

Since a quantity of β-(2-thenoyl)-propionic acid was at hand from other work, the thiosemicarbazone of this ketoacid was prepared.

The thiosemicarbazones did not possess significant antitubercular properties. However, two of the O-substituted hydroxylamines gave the following antitubercular activities: O-benzylhydroxylamine hydrochloride, active at 5 mg. %; O-2-phenoxyethylhydroxylamine hydrochloride, active at 1.25 mg. %. Both of these derivatives were active at 10 mg. % in the presence of bovine serum. The LD_{50} (mice) for these substances were 0.36 mg./g. and 0.26 mg./g., respectively. The hydroxylamines also exhibited a slight pressor activity.

Experimental

o-2-**Phenoxyethyl Acetoxime.**—This material was prepared by the condensation of 2-phenoxyethyl bromide and the sodium salt of acetoxime; b.p. 126–128° (4 mm.), $n^{20}D$ 1.5120.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.82; N, 7.25. Found: C, 68.5; H, 7.91; N, 7.34.

O-2-Phenoxyethyl Hydroxylamine Hydrochloride.[7]—O-2-Phenoxyethyl acetoxime was hydrolyzed by refluxing for four hours with 10% hydrochloric acid. A 63% yield of product was obtained, m.p. 172° (dec.).

Anal. Calcd. for $C_8H_{12}ClNO_2$: Cl, 18.7; N, 7.39. Found: Cl, 18.6; N, 7.52.

O-Benzylhydroxylamine Hydrochloride.—This compound was prepared as above, m.p. 230–235° (dec.). Behrend[8] reported this salt to melt at 226–235° (dec.).

O-Isoamyl Acetoxime.—This oxime was prepared in 50% yield as in previous experiments; b.p. 154–155° (66–69° (25 mm.)), $n^{20}D$ 1.4230.

Anal. Calcd. for $C_8H_{17}NO$: N, 9.78. Found: N, 9.61.

O-Isoamylhydroxylamine Hydrochloride.—Hydrolysis of the above oxime with 10% hydrochloric acid gave a 28% yield of desired product, m.p. 173–174° (dec.).

Anal. Calcd. for $C_5H_{17}ClNO$: Cl, 25.4; N, 10.0. Found: Cl, 25.5; N, 10.3.

O-2-(4-Ethoxyphenoxy)-ethyl Acetoxime.—The desired substance was obtained in 18% yield by the prior procedure, b.p. 150–153° (5 mm.).

Anal. Calcd. for $C_{13}H_{19}NO$: N, 6.86. Found: N, 6.95.

O-2-(4-Ethoxyphenoxy)-ethylhydroxylamine Hydrochloride.—The acid hydrolysis of the corresponding acetoxime gave a 35% yield of the expected salt, m.p. 188–192° (dec.).

Anal. Calcd. for $C_{10}H_{16}ClNO_3$: Cl, 15.2; N, 6.01. Found: Cl, 15.4; N, 6.20.

The following general procedure was used to prepare the thiosemicarbazones (II) and the data are recorded in Table I.

A solution of 5 g. of the ketone, 1.26 g. of thiosemicarbazide and 3 ml. of concd. sulfuric acid in 125 ml. of 95% ethanol was refluxed for six hours. The mixture was filtered while hot and the filtrate allowed to cool overnight. The lemon-yellow to cream-colored product was recrystallized from the appropriate solvent.

(1) T. Urbanski, *Nature*, **166**, 267 (1950).
(2) T. Urbanski, S. Slopek and S. Venulet, *ibid.*, **168**, 29 (1951).
(3) T. S. Gardner, E. Wenir and F. A. Smith, THIS JOURNAL, **73**, 5455 (1951).
(4) J. Bernstein, *et al.*, *ibid.*, **73**, 906 (1951).
(5) H. Bauer, *ibid.*, **73**, 5862 (1951).
(6) P. Truitt, R. Stead, L. M. Long and W. J. Middleton, *ibid.*, **71**, 3511 (1949).
(7) P. Truitt, L. M. Long and M. Mattison, *ibid.*, **70**, 1989 (1948).
(8) Behrend, *Ann.*, **257**, 207 (1890).

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The Stereochemistry of the Reaction of γ-Methoxy Acids with Thionyl Chloride

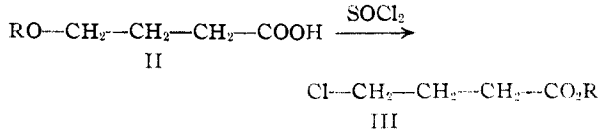
BY KENNETH B. WIBERG

RECEIVED JANUARY 19, 1952

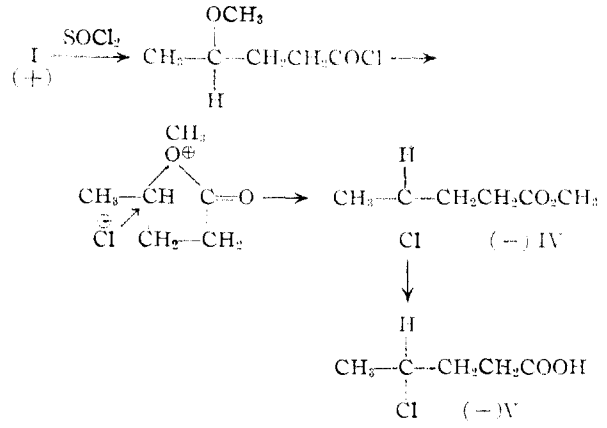
The stereochemical relationship between (+)-γ-methoxyvaleric acid (I) and the (+)-methyl alkyl carbinols, which has recently been determined,[1] permits one to determine the stereochemistry of the reaction of the γ-methoxy acids with thionyl chloride. It has previously been shown that the γ-alkoxybutyric acids (II) give γ-chloro-

(1) W. E. Doering and R. W. Young, THIS JOURNAL, **74**, 2997 (1952).

butyric esters (III) when treated with warm thionyl chloride.[2]



Levene and Haller[3] have shown that (+)-2-hexanol has the same configuration as (+)-γ-chlorovaleric acid (V), the acid derived from the expected ester (IV). Since it has now been found that (+)-I gives the ester of (−)-V, it is apparent that the reaction produced an inversion at the optically active center, thus confirming the mechanism previously suggested.[2b]



Experimental[4]

Methyl 4-Chlorovalerate (IV).—To 26 g. (0.2 mole) of (+)-I,[1] ($[\alpha]^{24}D$ +1.53°, neat, l = 1) was added 30 g. of thionyl chloride, and the mixture was heated to reflux for one hour. After cooling, the mixture was added to water and extracted with ether. The ether extract was washed with 10% sodium carbonate solution, dried over sodium sulfate and distilled giving 20 g. (67%) of methyl 4-chlorovalerate, b.p. 73–75° at 15 mm., $n^{25}D$ 1.4298, d^{25} 1.063, $[\alpha]^{25}D$ −2.07° (neat, l = 1); MD, calcd. 36.53, found 36.68.

Anal. Calcd. for $C_6H_{11}O_2Cl$: C, 47.85; H, 7.36; Cl, 23.54. Found: C, 47.77; H, 7.34; Cl, 23.25.

IV was hydrolyzed by the procedure of Levene and Mori[5] giving 4-chlorovaleric acid (V) having b.p. 120–122° at 20 mm., $\alpha^{25}D$ −2.36° (neat, l = 1).

A sample of (±)-IV,[6] prepared by the interaction of γ-valerolactone, methanol and hydrogen chloride according to the method of Levene and Mori[5] was found to have b.p. 73–75° at 15 mm., $n^{25}D$ 1.4299, d^{25} 1.061. The infrared spectra of IV prepared by the two procedures were identical.

Anal. Calcd. for $C_6H_{11}O_2Cl$: C, 47.85; H, 7.36; Cl, 23.54. Found: C, 47.68; H, 7.31; Cl, 23.40.

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(2) (a) F. F. Blicke, W. B. Wright and M. F. Zienty, THIS JOURNAL, **63**, 2488 (1941); (b) V. Prelog and S. Heimbach-Juhasz, *Ber.*, **74B**, 1702 (1941).

(3) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **83**, 591 (1929). On the basis of our present knowledge of the Walden inversion, their work must be corrected to state that the reaction between an aliphatic secondary alcohol and a phosphorus halide gives inversion rather than retention of configuration.

(4) Analyses were performed by O. Schwarzkopf and T. Hinton.

(5) P. A. Levene and T. Mori, *J. Biol. Chem.*, **78**, 1 (1928).

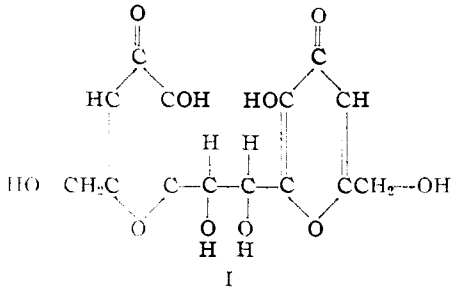
(6) Kindly supplied by Dr. R. W. Young.

The Condensation of Kojic Acid with Glyoxal[1]

BY L. L. WOODS

RECEIVED FEBRUARY 18, 1952

The easy condensation of kojic acid with glyoxal produces a compound which exhibits more promise of becoming an important chemical intermediate than any other produced in this series of experiments.[2,3] The fact that 1,2-bis-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-ethylene glycol (I) formed during the reaction is sensitive to strong acidic reagents and undergoes a 1,2-shift typical of the pinacol rearrangement[4] was expected; as was the



I

fact that thionyl chloride would convert the hydroxy methyl groups to stable chloromethyl groups, whereas the glycolic hydroxyls when removed by chlorine exhibited no such stability in the presence of water. A similar observation has been made before[2] and an explanation has been advanced by Stodola.[5]

Experimental[6]

1,2-Bis-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-ethylene Glycol (I).—A mixture of 10 ml. of 30% glyoxal, 50 ml. of absolute ethanol and 7.1 g. of kojic acid was heated to boiling—cooled slightly—and 1 g. of potassium bicarbonate was added. The stoppered flask was set aside and the mixture allowed to react overnight. The next day the flask was filled with yellow-orange crystals which when recrystallized from ethanol produced 4.5 g. of yellow needles which melted at 147–149°. During the melting point determination some sublimate was formed which melted at 155.5–156.5°. The sublimate was probably due to thermal rearrangement of (I) to form a small amount of (II). Compound (I) gave a very deep red coloration to dilute solutions of ferric chloride. The compound gave no test with Schiff reagent.

Anal. Calcd. for $C_{14}H_{14}O_{10}$: C, 49.12; H, 4.09. Found: C, 49.40; H, 4.30.

1-Oxy-1,2-bis-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-ethane (II).—Three grams of (I) was placed in 10 g. of cold concentrated sulfuric acid and allowed to stand 24 hours. The viscous mass was diluted with 100 ml. of water and neutralized with sodium bicarbonate. The rearranged compound was obtained by repeated extractions with ethyl acetate. The extract was dried with anhydrous sodium sulfate and the solvent evaporated, giving 0.8 g. of yellow prisms. Recrystallization from ethanol produced crystals

(1) The author wishes to express his gratitude to the Corn Products Sales Corporation for the kojic acid used in these experiments and to the Research Corporation for a Frederick Cottrell Grant-in-aid to continue this investigation.

(2) L. L. Woods, THIS JOURNAL, **72**, 4322 (1950).

(3) L. L. Woods, *ibid.*, **74**, 1106 (1952).

(4) G. W. Wheland, "Advanced Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1949, p. 452; E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 45.

(5) F. H. Stodola, THIS JOURNAL, **73**, 5912 (1951).

(6) All analyses were performed by Dr. Carl Tiedcke. All melting points were made on a Fisher-Johns melting point assembly.