Then 4600 g. of sodium amalgam made from 90.2 g. (3.92 mole) of sodium and 4510 g. of mercury by direct union of the elements was added at the rate of 400 g. every five minutes. Concurrently, an additional 800 g. of boric acid was added in portions alternating with those of amalgam. During the entire course of the operation the temperature was held at 13–15° by judicious addition of ice and very efficient mechanical stirring was provided. The reduction took about two hours. After all the reactants were added, the fluffy yellow Schiff base and excess toluidine were filtered off, acidified with cold 18 *N* sulfuric acid and steam distilled. The distillate was cooled to about 10° and filtered. No appreciable amount of aldehyde remained in the filtrate. The yield of II so obtained was 80.0 g., 57.0%; m. p. 67–68°.

The *p*-toluidine was recovered almost quantitatively from the residue from the steam distillation by carefully making it alkaline with 40% sodium hydroxide and continuing the distillation. The mercury was also recovered after decanting off the Schiff base and could be used to prepare more amalgam after being washed and dried.

Descriptive Information on the Aldehydes.—The aldehydes are stable, colorless crystalline solids. II and IV are volatile in steam and give a purple ferric complex. III is not volatile in steam and gives a sherry ferri-complex. All give a positive Schiff test, which soon fades. They reduce cold Tollens reagent only after several hours. Warming gives a black granular deposit of silver. None reduce boiling Fehling solution.

Discussion

Attempts to prepare II by the N-methylformanilide reaction[8] were entirely unsuccessful. The hexamethylenetetramine reaction[9] gave a 0.5% yield. A synthesis based upon the oxidation of 2-fluoro-6-Δ^1-propenylphenol[10] gave somewhat better yields but was still unsatisfactory.

The reaction conditions described for the synthesis of I, II, III and V were arrived at by systematic investigation of the effects of varying molar ratios, temperature, time, etc. Deviation from them may result in seriously lowered yields.

The structures of the isomeric II and III, both of which were obtained in the Reimer–Tiemann reaction were assigned by showing that II reacts with ethylenediamine to form a Schiff base which forms a chelate with cupric ion, while III does not.

The structure of V was established by a mixed melting point showing its identity with the acid formed by oxidation of III synthesized by the Reimer–Tiemann reaction. The oxidation was accomplished by making the oxime of the aldehyde, dehydrating it to the nitrile and hydrolyzing the nitrile. A specimen of I was prepared by silver oxide oxidation of II and shown to melt at the same temperature as the Kolbe–Schmidt product.

Acknowledgment.—We are indebted to Mr. Charles W. Koch for the carbon–hydrogen analyses and to Mr. Richard R. Holmes for working out the procedure for assaying the mixed acids in the Kolbe–Schmidt product and for carrying out a number of these analyses.

Summary

The preparation of 3-fluorosalicyclic acid, 3-fluoro-4-hydroxybenzoic acid, 3-fluorosalicylaldehyde, 3-fluoro-4-hydroxybenzaldehyde and 5-fluorosalicylaldehyde, all hitherto unreported, has been accomplished and their synthesis is described.

BERKELEY, CALIFORNIA RECEIVED JULY 22, 1946

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[8] L. F. Fieser and J. E. Jones, THIS JOURNAL, **54**, 1666 (1942).

[9] V. C. Duff, *J. Chem. Soc.*, 547 (1941).

[10] Developed by Richard R. Holmes and Dr. Warren G. Miller, unpublished.

[CONTRIBUTED FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Isomeric Esters Produced by the Dehydration of Ethyl 3-Hydroxy-2,3-dimethylbutanoate

BY RALPH C. HUSTON AND GORDON L. GOERNER

In the preparation of a certain alcohol in our laboratory, it became necessary to prepare ethyl 2,3-dimethylbutanoate (IV). The path chosen was through the Reformatsky[1] reaction, using propanone and ethyl 2-bromopropanoate to prepare ethyl 3-hydroxy-2,3-dimethylbutanoate (I). The latter was dehydrated to the unsaturated esters (II and III) which were then reduced to IV.

$$\underset{\text{I}}{\mathrm{(CH_3)_2C(OH)CH(CH_3)COOC_2H_5}} \longrightarrow$$

$$\underset{\text{II}}{\mathrm{CH_2{=}C(CH_3)CH(CH_3)COOC_2H_5}}, \text{ and } \underset{\text{III}}{\mathrm{(CH_3)_2C{=}C(CH_3)COOC_2H_5}}$$

$$\text{II or III} \xrightarrow[\text{Pt}]{\mathrm{H_2}} \underset{\text{IV}}{\mathrm{(CH_3)_2CHCH(CH_3)COOC_2H_5}}$$

Shriner[2] states that β-hydroxy esters are generally unstable, many of them dehydrating upon distillation. Ester I, which contains a tertiary hydroxyl group, proved to be exceptionally stable. Dehydration by dry hydrogen chloride[3] failed completely. Iodine[4] likewise proved unsatisfactory, 10 g. being required to dehydrate one mole of the ester. Phosphorus pentoxide[5] in benzene gave satisfactory results.

Only one unsaturated ester corresponding to compounds II and III is recorded in the literature[6] with a boiling point of 153 to 157°.

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[1] (a) Gilaroff, *J. Russ. Phys.-Chem. Soc.*, **28**, 501 (1896); (b) Perkin and Thorpe, *J. Chem. Soc.*, 1482 (1896).

[2] "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 11.

[3] Natelson and Gottfried, THIS JOURNAL, **61**, 970 (1939).

[4] Whitmore and Laughlin, *ibid.*, **54**, 4392 (1932); Hibbert, *ibid.*, **37**, 1748 (1915).

[5] Kon and Nargund, *J. Chem. Soc.*, 2461 (1932).

[6] Merling and Welde, *Ann.*, **366**, 140 (1909); v. Auwers and Eisenlohr, *J. prakt. Chem.*, [2] **82**, 167 (1910); Jupp, Kon and Lockton, *J. Chem. Soc.*, 1642 (1928).

Difficulty is frequently encountered in separating mixtures of α,β and β,γ unsaturated esters. We found, however, that esters II and III were separated readily by distillation. Their boiling points are 151° and 169° at 733 mm., or a difference of 18°. These esters may be considered

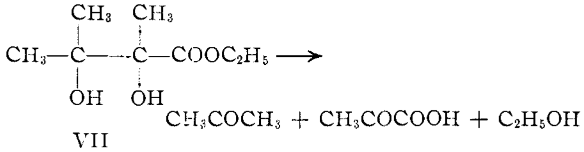
$$CH_2{=}C(CH_3)CH(CH_3)_2 \quad \text{V} \qquad (CH_3)_2C{=}C(CH_3)_2 \quad \text{VI}$$

derivatives of 2,3-dimethyl-1-butene (V) and 2,3-dimethyl-2-butene (VI) in which a methyl group of the hydrocarbon has been replaced by a carbethoxy group. These two hydrocarbons boil respectively at 55.8 and 73.3°[7] or a difference of 17.5°. If ester II is analogous to hydrocarbon V, and ester III to hydrocarbon VI, ester II should boil at the lower temperature. By peculiar coincidence, the difference between boiling points of the esters is almost identical with the difference between the boiling points of the hydrocarbons.

2,3-Dimethyl-2-butene contains approximately 1.4 kcal. per mole less energy than 2,3-dimethyl-1-butene[8] and it is less readily reduced in the presence of platinum catalyst. The corresponding ester, ethyl 2,3-dimethyl-2-butenoate is also much more difficultly reduced than its isomer. This stability may be explained by the lower relative energy of ester III which results from the three methyl groups on doubly bonded carbons and from the conjugation of the carbon–carbon double bond with the carbon–oxygen double bond of the carbethoxy group. Both esters are reduced to ethyl 2,3-dimethylbutanoate.

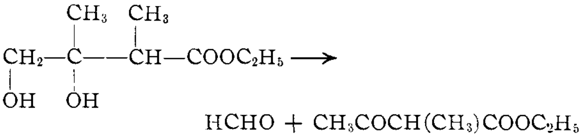
The difference between the boiling points of the acids is much smaller than the difference in boiling points of the esters or hydrocarbons. 2,3-Dimethyl-3-butenoic acid boils at 108° (25 mm.)[9] and 2,3-dimethyl-2-butenoic acid at 114–115° (27 mm.).[10]

Both esters were degraded by hydroxylating them to the glycols[11] and then splitting them into the aldehydes and ketones by means of "perchlorato-cerate" ion in perchloric acid solution.[12] The high boiling ester gave a glycol (VII) which


VII

$$CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}-\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}-COOC_2H_5 \longrightarrow CH_3COCH_3 + CH_3COCOOH + C_2H_5OH$$

yielded propanone and 2-ketopropanoic (pyruvic) acid. These were characterized through the 2,4-dinitrophenylhydrazones. The low boiling ester


VIII IX

$$\underset{\underset{OH}{|}}{CH_2}-\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}-\overset{\overset{CH_3}{|}}{CH}-COOC_2H_5 \longrightarrow HCHO + CH_3COCH(CH_3)COOC_2H_5$$

gave a glycol (VIII) which should yield methanal and ethyl 3-keto-2-methylbutanoate (IX). However, the methanal is oxidized to carbon dioxide and water. The solution containing compound IX gave butanone upon alkaline hydrolysis. This was characterized as the 2,4-dinitrophenylhydrazone.

Experimental

Preparation of ethyl 3-hydroxy-2,3-dimethylbutanoate (I) was by the Reformatsky reaction, a modification of the procedure of Perkin and Thorpe.[1b] The propanone was dried over anhydrous potassium carbonate and the benzene over sodium. Ethyl 2-bromopropanoate was obtained from Eastman. Ten-mesh zinc was cleaned and dried by the method of Fieser and Johnson.[13]

In a typical two mole run, 164 g. of zinc (2.5 moles) was placed in a 3-liter three-necked flask equipped with mechanical stirrer, reflux condenser, thermometer and one-liter separatory funnel. A mixture of 50 ml. of benzene, 17 g. of propanone and 12 g. of ethyl 2-bromopropanoate was added, followed by 5 ml. of ethylmagnesium bromide. The flask was heated with a burner until vigorous refluxing began. Then a mixture consisting of the rest of 362 g. (2 moles) of ethyl 2-bromopropanoate, 174 g. (3 moles, an excess) of propanone and 450 ml. of benzene was added at a rate to maintain reflux. The addition was complete in thirty-five minutes, with an average temperature of 75°.

After refluxing for one and one-half hours, the contents of the flask was cooled and poured, with vigorous stirring, into 1200 ml. of ice-cold 10% sulfuric acid. When hydrolysis was complete, the benzene layer was removed and the aqueous layer extracted thrice with 50-ml. portions of benzene. The combined benzene extracts were washed with 100 ml. of cold 5% sulfuric acid, 50 ml. of 10% sodium carbonate, 50 ml. of water and dried over anhydrous sodium sulfate.

Dehydration of Ethyl 3-Hydroxy-2,3-dimethylbutanoate.[1]—This was accomplished without isolating the hydroxy ester. The dried benzene solution was filtered into a 3-liter flask and distilled until the distillate became clear. To the benzene solution was then added 225 g. of phosphorus pentoxide[5] and the solution was refluxed for four hours. After cooling, the benzene layer was decanted and the solid rinsed with 200 to 300 ml. of dry benzene.

The combined benzene extracts were fractionated under diminished pressure through a two-foot Fenske type column packed with $^3/_{32}$-inch glass helices. Thirty-three grams of ethyl propanoate, boiling point 41° at 83 mm., was obtained.

The yield of ethyl 2,3-dimethyl-3-butenoate (II), boiling at 84.5 to 85.5° at 83 mm., was 70 g. (25%); micro boiling point 151° at 733 mm., n^{20}_D 1.4210, d^{20}_4 0.8958.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.69; H, 9.92. Found: C, 67.75; H, 9.75.

Fifty-four grams (19%) of ethyl 2,3-dimethyl-2-butenoate (III) was obtained at 99 to 99.5° at 81.5 mm.; micro boiling point 169° at 733 mm., n^{20}_D 1.4430, d^{20}_4 0.9199.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.69; H, 9.92. Found: C, 67.84; H, 9.90.

Total yield of unsaturated esters, including the intermediate fraction, was 130 g. or 46% based on the bromo ester.

Reduction of the Unsaturated Esters.—One-tenth mole of the ester, 100 ml. of ethanol and 0.2 g. of the catalyst

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[7] Egloff, "Physical Constants of Hydrocarbons," Vol. I, Reinhold Publishing Corporation, New York, N. Y., 1939, pp. 194 and 196.

[8] Kistiakowsky, Ruhoff, Smith and Vaughan, THIS JOURNAL, **58**, 137 (1936).

[9] Kon and Speight, *J. Chem. Soc.*, 2730 (1926).

[10] Bardhan, *ibid.*, 2614 (1928).

[11] Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936).

[12] Smith and Duke, *Ind. Eng. Chem., Anal. Ed.*, **13**, 558 (1941); **15**, 120 (1943).

[13] Fieser and Johnson, THIS JOURNAL, **62**, 576 (1940).

and 50 lb. of hydrogen pressure were used in each case. With ester II and platinum oxide catalyst, the reaction was complete in twenty minutes; with palladous oxide, the reaction required four hours. Ester III was reduced in two to four hours using platinum and, incompletely, after seven hours with palladium.

The saturated ester (IV) was recovered upon fractionation of the alcoholic solution and identified by its boiling point, density and refractive index.[14]

Degradation of High Boiling Ester (III).—Seven grams (0.05 mole) of the ester, boiling at 169°, was treated with 0.05 mole of hydrogen peroxide and 2 ml. of osmium tetroxide catalyst according to the procedure of Milas and Sussman.[11] The gray solution was distilled under diminished pressure. The fraction boiling from 62 to 73° contained the glycol (VII). This was treated with successive small portions of perchlorato-cerate ion in perchloric acid, "Ceric perchlorate,"[12] (10 g. $(NH_4)_2Ce(NO_3)_6$ in 50 ml. of 15 to 20% perchloric acid) until a red color was no longer formed. Air was blown through the warmed solution and then into a test-tube containing 2,4-dinitrophenylhydrazine dissolved in dilute perchloric acid. The bright yellow crystals which precipitated were collected, washed and crystallized twice from ethanol; m. p. 124–126°. A mixed melting point with an authentic sample of propanone-2,4-dinitrophenylhydrazone gave no depression.

After all the propanone had been blown out of the reaction mixture, addition of a perchloric acid solution of 2,4-dinitrophenylhydrazine produced a precipitate which melted at 221.5 to 223.5° after one crystallization from dioxane–ethanol. A mixed melting point with an authentic sample of 2-keto-propanoic acid 2,4-dinitrophenylhydrazone (m. p. 221.5–223°) gave no depression.

Degradation of Low Boiling Ester (II).—Hydroxylation of the ester boiling at 151° was carried out as above. However, the glycol began to decompose at 70° at 13 mm. Hence, the residue was treated with the "ceric perchlorate" as previously described. As soon as the "ceric perchlorate" no longer gave a red color, the solution was made alkaline with potassium hydroxide and refluxed three to four hours. Air was blown through the solution as before. The precipitated 2,4-dinitrophenylhydrazone, upon recrystallization from ethanol, melted at 108–109°. No depression in the melting point was observed when this compound was mixed with an authentic sample of butanone 2,4-dinitrophenylhydrazone.

Acknowledgment.—We wish to express our appreciation to Dr. Frederick R. Duke for his suggestions concerning the use of "ceric perchlorate" in splitting the glycols obtained during this investigation.

Summary

Ethyl 3-hydroxy-2,3-dimethylbutanoate has been dehydrated to ethyl 2,3-dimethyl-2-butenoate and ethyl 2,3-dimethyl-3-butenoate. These have been isolated and their physical constants determined.

The structure of these unsaturated esters has been assigned on the basis of the ketones to which they have been degraded.

East Lansing, Michigan Received July 5, 1946

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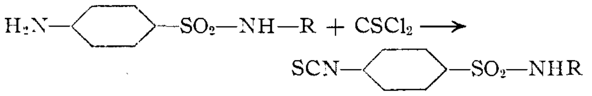
[14] Gorski, *J. Russ. Phys.-Chem. Soc.*, **45**, 167 (1912).

[Contribution from the Venable Chemical Laboratory of the University of North Carolina]

p-Substituted Phenyl Isothiocyanates and Some Related Thioureas

By R. L. McKee[1] and R. W. Bost

By use of the reaction between primary amines and thiophosgene,[2] sulfanilamide, sulfadiazine, sulfaguanidine, sulfacetamide, sulfapyridine and sulfathiazole have been converted into the corresponding isothiocyanates (Table I).

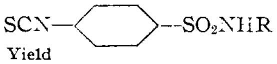


The isothiocyanates are quite stable in contact with water or dilute aqueous acids. They may be dissolved in cold, dilute alkali and reprecipitated unchanged by acid; prolonged solution in alkali brings about their decomposition.

Several of the isothiocyanates and the previously prepared[2] *p*-isothiocyanobenzoic acid were allowed to react with amines to form the corresponding thioureas (Table II).

Table I

p-Isothiocyanobenzenesulfonamides, SCN—⬡—SO₂NHR



Cpd.	R=	Sulfonamide	Moles	Cryst. from	Yield pure product, %	M. p., °C.	Formula	Analyses, % sulfur	
								Calcd.	Found
I	Hydrogen	Sulfanilamide	0.12	Acetone–water	89	212–214 (dec.)	$C_7H_6N_2O_2S_2$	29.93	29.84
II	Acetyl	Sulfacetamide	.095	Acetone–ligroin	88	156–159	$C_9H_8N_2O_3S_2$	25.02	24.98
III	Carboxamidine	Sulfaguanidine	.035	Acetone–water	76	216–217	$C_8H_8N_4O_2S_2$	25.02	24.81
IV	2-Pyridyl	Sulfapyridine	.16	Acetone–dioxane	90	198–200 (dec.)	$C_{12}H_9N_3O_2S_2$	22.01	22.07
V	2-Thiazolyl	Sulfathiazole	.16	Acetone	98	239–242 (dec.)	$C_{10}H_7N_3O_2S_3$	32.34	32.19
VI	2-Pyrimidyl	Sulfadiazine	.064	Dioxane–water	95	237–240 (dec.)	$C_{11}H_8N_4O_2S_2$	21.93	22.02

The exclusive attack on the amino nitrogen is indicated by the high yields of products which have retained the characteristic alkali solubility of sulfonamides but are no longer acid soluble.

Experimental

Since identical procedures were employed for each of the two groups comprising compounds I-VI and VII-XII, only one preparation from each group is described in detail.

4-Isothiocyanobenzenesulfonamide (I).—Sulfanilamide (20 g., 0.12 mole) was dissolved in 200 cc. of water con-

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[1] The Wm. S. Merrell Co., Postdoctoral Fellow.

[2] Browne and Dyson, *J. Chem. Soc.*, 178 (1934).