Sulfuric acid hydrolysis of *m*-nitrophenylthioacetmorpholide gave a 22% yield of *m*-nitrophenylacetic acid which melted at 117–119° after recrystallization from water; its m. p. is variously reported[26] as 117 to 120°.

Use of Other Amines.—The standard procedure described for morpholine and styrene was used in all the comparative runs made with other amines and styrene. In only four cases were the thioamides isolated and purified. The results are summarized in Table II in the text.

Use of Sulfur and Aqueous Ammonia.—The experiments summarized in Table III in the text were all carried out as previously described,[1] on a 0.010 molar scale, except that 0.020 mole of sulfur and 0.050 mole of ammonia were substituted for ammonium polysulfide. Each amide was identified by melting point and mixed melting point determination with an authentic sample of the amide.

Summary

It has been shown that the Willgerodt reaction, in its morpholine modification, is applicable to aromatic compounds which contain as ring substituents hydroxy-, acetoxy-, amino-, acetamido- and nitro-groups.

The use of the reaction under reflux conditions has been extended to a number of amines other than morpholine.

The sulfur-aqueous ammonia procedure has been applied to compounds of diverse types.

RENSSELAER, NEW YORK RECEIVED JULY 13, 1946

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[26] Gabriel and Borgmann, *Ber.*, **16**, 2064 (1883); Salkowski, *ibid.*, **17**, 507 (1884).

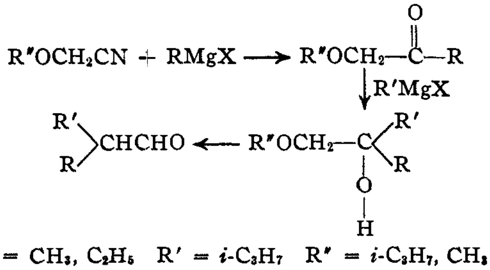
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY, AND THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

2,3-Dimethylbutanal and 2-Ethyl-3-methylbutanal

BY RODERICK A. BARNES AND WALTER M. BUDDE[1]

2,3-Dimethylbutanal and 2-ethyl-3-methylbutanal were first obtained by the ozonolysis of ergosterol[2] and stigmasterol,[3] respectively. The former aldehyde has been synthesized, on a small scale and in unstated yields, by hydrolysis of 1,2-dibromo-2,3-dimethylbutane[4] and by the decarboxylation of 3,4-dimethyl-2,3-epoxypentanoic acid.[5] An attempt to prepare 2-ethyl-3-methylbutanal from the corresponding epoxy-acid failed completely, and the Rosenmund reduction of the appropriate acid chloride resulted in a 7% yield.[6]

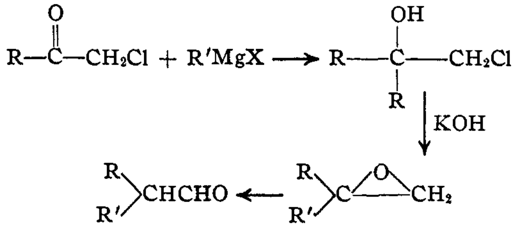
The first method investigated in this work was similar to that originally employed by Béhal and Sommelet[7] and by Stoermer[8] for the preparation of some dialkylacetaldehydes. In this method, the alkyl ether of a substituted ethylene glycol was heated with dilute acids or with anhydrous oxalic acid. Application of this method to the preparation of 2,3-dimethylbutanal and 2-ethyl-3-methylbutanal involved the following reactions



$R = CH_3, C_2H_5 \quad R' = i\text{-}C_3H_7 \quad R'' = i\text{-}C_3H_7, CH_3$

The reaction of α-alkoxynitriles with Grignard reagents has been investigated by Henze and coworkers,[9] who have reported yields of 44–48%. In some preparations, it was possible to raise the yield to 55–60% by addition of the nitrile to the Grignard reagent at −50°. The second step, the reaction of the Grignard reagent with the α-alkoxyketone, with one exception, gave yields of 50–60%, while the reaction of the glycol-monoalkyl ethers with either 10% aqueous hydrochloric acid or with anhydrous oxalic acid produced the desired aldehydes in yields of 60–75%.

The second method for the preparation of unsymmetrical dialkylacetaldehydes was based on the rearrangement of an oxide, as follows



$R = CH_3, R' = i\text{-}C_3H_7$

The reaction of isopropylmagnesium bromide with chloroacetone has been reported[10] to yield 47.5% of the chlorohydrin. In the present work, better over-all yields of the oxide were obtained by treating the crude chlorohydrin directly with powdered potassium hydroxide. The oxide reacted with hydrochloric acid to produce the desired aldehyde in a 61% yield. This synthesis was found to be most convenient for the preparation of 2,3-dimethylbutanal since the whole series of reactions could be carried out without isolating the intermediates. The aldehyde (purified through

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[1] A large part of the work on 2,3-dimethylbutanal was taken from a Senior Thesis by W. M. Budde, August, 1945, U. of Minn. Present address: Chemistry Department, Indiana University Bloomington, Indiana.

[2] Reindel and Kipphan, *Ann.*, **493**, 181 (1932).

[3] Guiteras, *Z. physiol. Chem.*, **214**, 89 (1933).

[4] Whitmore and Meunier, THIS JOURNAL, **63**, 2199 (1941).

[5] Brunner and Farmer, *J. Chem. Soc.*, 1039 (1937).

[6] Dirscherl and Nahm, *Ber.*, **76B**, 635 (1943).

[7] Béhal and Sommelet, *Bull. soc. chim.*, [3] **31**, 305 (1904).

[8] Stoermer, *Ber.*, **39**, 2288 (1906).

[9] Henze and Rigler, THIS JOURNAL, **56**, 1350 (1934).

[10] Chalmers, *Trans. Roy. Soc. Can.*, [3] **22**, III, 76 (1928).

TABLE I

$R''OCH_2CN + RMgX \longrightarrow R''OCH_2COR$

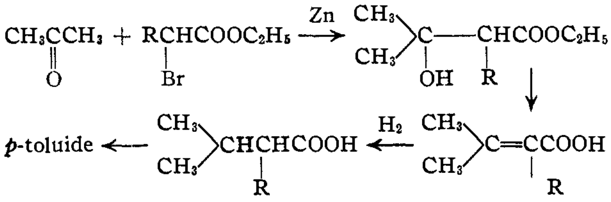
					Analyses of DPH, %			
					Carbon		Hydrogen	
R	R"	B. p., °C.	Yield, %	M. p. of DPH,^{a} °C.	Calcd.	Found	Calcd.	Found
C_2H_5	CH_3	129–133	59	197–198	46.81	47.08	5.00	5.14
i-C_3H_7	CH_3	140–144	30	162–163	48.64	48.45	5.44	5.27
CH_3	i-C_3H_7	139–142	53	141–142	48.64	48.53	5.44	5.56
i-C_3H_7	i-C_3H_7	155–160	17	87–88	51.84	52.03	6.22	6.52

[a] DPH = 2,4-dinitrophenylhydrazone.

the bisulfite addition product) was obtained in an over-all yield of 14–16%.

Isolation of the pure aldehydes was somewhat difficult since they were not readily separable from ether or petroleum ether by distillation. Furthermore these aldehydes were rapidly oxidized by air to the corresponding acids. Carefully fractionated samples of the aldehydes, to which small amounts of hydroquinone were added, remained unchanged for several weeks when kept in the refrigerator under nitrogen, as was shown by quantitative conversion to the 2,4-dinitrophenylhydrazones.

Since no satisfactory physical constants have been reported for these aldehydes, and no authentic derivatives were available, the structures[11] were proved by oxidation of the aldehydes to the corresponding acids, which were identified by conversion to the *p*-toluides. Both the acids and the toluides were prepared by the following unequivocal synthesis



R = CH_3, C_2H_5

Acknowledgment.—The authors are indebted to Doris E. Barnes, Lathrop Baker and Lois E. May for the microanalyses reported here.

Experimental[12]

Alkoxyacetonitriles. A. Methoxyacetonitrile.—This substance was prepared by the method of Scarrow and Allen[13] and also by the reaction between cuprous cyanide and chloromethyl ether.[9] The latter method was found to be most reliable; in all preparations yields of 70–75% resulted.

B. Isopropoxyacetonitrile.—Powdered cuprous cyanide (320 g., 3.58 moles) was slowly added, with mechanical stirring, to chloromethyl *i*-propyl ether[14] (390 g., 3.6 moles) and iodine (1 g.). A few minutes after the initial addition of cuprous cyanide the reaction mixture darkened and heat was evolved. The cuprous cyanide was added at such a rate that the temperature of the reaction mixture remained at 80–90°; no external heating or cooling was necessary. The reaction was completed by heating on the steam-bath for three hours with continued stirring. The product was distilled directly from the reaction flask, first at atmospheric pressure and finally at 12 mm., to remove the last traces of product from the solid cake. On redistillation through a 15-cm. Widmer column there was obtained 258 g. (72%) of material which boiled at 145–146°; $n^{26}D$ 1.3943.

Anal. Calcd. for C_5H_9ON: C, 60.58; H, 9.15. Found: C, 60.33; H, 8.89.

Alkoxyketones.—A modification of the method of Henze and Rigler[9] was used and is illustrated by the following typical example.

1-Methoxybutanone-2.—Methoxyacetonitrile (71 g., 1 mole) dissolved in dry ether (250 ml.) was added dropwise to a well-stirred solution of ethylmagnesium bromide (prepared in the usual manner from 30 g. of magnesium, 150 g. of ethyl bromide and 1000 ml. of dry ether). The solution was maintained at −50 ± 10° in a bath of Dry Ice and acetone during the addition. Toward the end of the addition a dark oil separated which soon solidified to a gray powdery solid. After the addition was complete the reaction mixture was gradually allowed to attain room temperature and finally was allowed to stand for eighteen hours. The mixture was cooled with ice and decomposed by addition of dilute hydrochloric acid (water 220 ml., concentrated hydrochloric acid 220 ml.). The ether layer was separated and the aqueous layer was extracted with four 75-ml. portions of ether. The combined ether solutions were washed with water (150 ml.), and finally dried over sodium sulfate. The ether was removed by distillation through a 45-cm. column packed with helices and the residue was fractionated at atmospheric pressure using a 10-cm. column. There was obtained 60.4 g. (59%) of the ketone which boiled at 129–133°.

1-Methoxy-2,3-dimethylbutanol-2.—A solution of isopropylmagnesium bromide, prepared from isopropyl bromide (40 g.), and magnesium (7.3 g.) in dry ether (200 ml.), was cooled in an ice–salt-bath while methoxyacetone (31 g.) was added dropwise with stirring. When the addition was complete the reaction mixture was allowed to warm up and finally was stirred for one hour at room temperature. The reaction flask was cooled and a saturated solution of ammonium chloride (75 g.) in water was added with stirring. The ether layer was separated, washed with water, dried over sodium sulfate, and the ether was removed on the steam-bath. The residue was distilled through a 10-cm. column packed with helices. The product weighed 19.7 g. (52%) and boiled at 32–41° (10 mm). Redistillation of this material through a 45-cm. Podbielniak column gave a pure product which boiled at 35–36° (10 mm.); $n^{23}D$ 1.4202.

Anal. Calcd. for $C_6H_{16}O_2$: C, 63.59; H, 12.20. Found: C, 63.66; H, 12.17.

The procedure above outlines the experimental details for the reactions used in the preparation of the glycol monoalkyl ethers.

2,3-Dimethylbutanal.—**A.** 1-Methoxy-2,3-dimethyl-butanol-2 (14.5 g.) was heated at 100–105° for four hours with anhydrous oxalic acid (20 g.). The aldehyde was steam distilled from the reaction flask and the distillate

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[11] The aldehydes obtained by ozonolysis of the sterols, unlike those prepared in this work, would be expected to be optically active. The fact that Reindel and Kipphan, reference 2, isolated a racemic aldehyde is readily explained by the observations of Badin and Pacsu, THIS JOURNAL, 67, 1353 (1945), who report that (+)2-methylbutanal is rapidly racemized in either alkaline or acid-solution.

[12] All melting points and boiling points are uncorrected.

[13] Scarrow and Allen, "Organic Syntheses," Coll. Vol. II, p. 387.

[14] Stappers, *Rec. trav. chim.*, 24, 256 (1905).

TABLE II

$R''OCH_2COR + R'MgX \longrightarrow R''OCH_2C(OH)RR'$

R	R′	R″	B. p. °C.	B. p. Mm.	Refr. index	Yield, %	Analyses, % Carbon Calcd.	Analyses, % Carbon Found	Analyses, % Hydrogen Calcd.	Analyses, % Hydrogen Found
CH_3	i-C_3H_7	CH_3	35–36	10	1.4202/23°	52	63.59	63.66	12.20	12.17
i-C_3H_7	CH_3	CH_3	60–61	28		48				
i-C_3H_7	C_2H_5	CH_3	54–55	11	1.4288/22°	58	65.71	65.67	12.41	12.18
C_2H_5	i-C_3H_7	CH_3	56–57	18		50				
CH_3	i-C_3H_7	i-C_3H_7	49–55	9	1.4167/25°	34	67.45	67.90	12.58	12.71

(200 ml.) was saturated with sodium bisulfite. This mixture was shaken for eighteen hours in a stoppered bottle, and the bisulfite insoluble material was extracted with ether. The aqueous layer was neutralized with sodium carbonate and steam distilled. The distillate (200 ml.) was saturated with sodium sulfate, and the aqueous layer was carefully removed. The wet aldehyde (8.1 g.) was dried over a little sodium sulfate and distilled from a small flask. The substance weighed 6.7 g. (61%) and boiled at 112–114°; n^{25}_D 1.3998; d_{25} 0.8097; MR_D calcd., 29.93; MR_D obs., 29.97.

Anal. Calcd. for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.94; H, 12.25.

The 2,4-dinitrophenylhydrazone melted at 123–124°.

Anal. Calcd. for $C_{12}H_{16}O_4N_4$: C, 51.42; H, 5.75. Found: C, 51.66; H, 5.74.

1-Isopropoxy-2,3-dimethylbutanol-2 could also be converted to 2,3-dimethylbutanal in 74% yield by refluxing with 10% hydrochloric acid for four hours.

B. A solution of chloroacetone (104 g.) dissolved in dry ether (400 ml.) was added dropwise (three hours) to a cooled (0°) solution of isopropylmagnesium bromide (prepared from 27.4 g. of magnesium, 140 g. of isopropyl bromide, and 500 ml. of dry ether). When the addition was complete the reaction mixture was stirred for one hour at room temperature. The cold (0°) mixture was decomposed by the gradual addition of water (200 ml.) followed by one equivalent of concentrated hydrochloric acid. The ether layer was separated and the aqueous layer was extracted with two 100-ml. portions of ether. The combined ether solutions were dried over sodium sulfate. To this dry solution of the crude chlorohydrin were added five 25-g. portions of freshly powdered potassium hydroxide. The flask was cooled and shaken after each addition to prevent the ether from boiling. The mixture was allowed to stand overnight and then was stirred vigorously for three hours. The solid material was filtered with suction, and the ether was removed from the filtrate by distillation through a 45-cm. column. The residue of crude oxide was refluxed for five hours with 10% hydrochloric acid (300 ml.). The aldehyde, steam distilled from this reaction mixture and purified as in part A, weighed 16.3 g. (14.5%) and boiled at 112–114°.

In one case the crude oxide was distilled; the material (19%) boiled at 96–101°. The oxide (4.7 g.) was rearranged by heating it with 10% hydrochloric acid, and the crude aldehyde was converted to the 2,4-dinitrophenylhydrazone, which weighed 7.4 g. (61%) and melted at 118–121°.

2-Ethyl-3-methylbutanal.—This aldehyde can be prepared in 60% yield from 1-methoxy-2-ethyl-3-methylbutanol-2 by procedure A of the previous preparation. The carefully fractionated aldehyde boiled at 133.5°[15] and had n^{25}_D 1.4086; d_{25} 0.8224; MR_D calcd., 34.55; MR_D obsd., 34.30.

Anal. Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.17; H, 12.22.

The pure 2,4-dinitrophenylhydrazone melted at 120–121°.

Anal. Calcd. for $C_{13}H_{18}O_4N_4$: C, 53.05; H, 6.16. Found: C, 53.26; H, 5.88.

2,3-Dimethylbutanoic Acid and 2-Ethyl-3-methylbutanoic Acid.—A. The appropriate aldehyde (2 g.) was shaken with silver oxide (6 g.) and 10% sodium hydroxide solution (50 ml.). The acid was liberated from its sodium salt and converted to the *p*-toluide. 2,3-Dimethylbutanoic acid *p*-toluide melted at 112.5–113°.[16]

Anal. Calcd. for $C_{13}H_{19}ON$: C, 76.06; H, 9.33. Found: C, 76.28; H, 9.19.

2-Ethyl-3-methylbutanoic acid *p*-toluide melted at 136–136.5°.[17]

Anal. Calcd. for $C_{14}H_{21}ON$: C, 76.67; H, 9.65. Found: C, 76.46; H, 9.38.

B. The acids were synthesized by means of the Reformatsky reaction from the appropriate α-bromoester (0.25 mole), zinc (20 g.) and acetone (16 g.) as described in "Organic Reactions."[18] Dehydration and hydrolysis of the hydroxyesters produced 2,3-dimethylbutene-2-oic acid (40%) and 2-ethyl-3-methylbutene-2-oic acid (11%), which were readily reduced by nickel and hydrogen in alkaline solution to the saturated acids. The *p*-toluides prepared from these acids were identical with those obtained in part A.

Summary

1. Two methods have been examined for the synthesis of unsymmetrical dialkylacetaldehydes.

2. These methods have been successfully applied to the preparation, in some quantity, of 2,3-dimethylbutanal and 2-ethyl-3-methylbutanal, two substances which have previously been obtained only in small amounts.

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RECEIVED MAY 17, 1946

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[15] Dirscherl and Nahm, ref. 6, report 67–70° as the boiling point of this substance. However, judging from our experience with this compound, it seems likely that they had a mixture of the aldehyde and ether.

[16] Crossley and Perkin, *J. Chem. Soc.*, **73**, 16 (1898), report 103–104° as the m. p. of the *p*-toluide of 2,3-dimethylbutanoic acid, whereas Hommelen, *Bull. soc. chim. Belg.*, **42**, 243 (1933), reports 112.6°.

[17] Perkin, *J. Chem. Soc.*, **77**, 91 (1900), reports 122–123° as the m. p. of the *p*-toluide of 2-ethyl-3-methylbutanoic acid whereas Dirscherl and Nahm, ref. 6, report 134–136°.

[18] Rupe, Steiger and Fiedler, cited by Shriner, "Organic Reactions," Vol. I, 1942, p. 17.