[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Studies on the Willgerodt Reaction. IV.[1] The Preparation of Nuclear-Substituted Phenylacetic Acids and Some Further Extensions of the Reaction[2]

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Although the Willgerodt reaction in one or more of its various forms has been carried out on halogen-substituted,[3,4,5] alkoxyl-substituted,[4,5,6,7] and alkylmercapto-substituted aromatic aliphatic ketones,[4] there have been no reports of its application to aralkyl ketones in which the aryl group is substituted by hydroxy-,[8] amino-, or nitro- groups. In fact, Schwenk and Bloch[5] have stated, without any elaboration, that the reaction in its morpholine modification seems not to be applicable to substances containing nitro-, amino-, hydroxy- or acetoxy-groups. In the present work it has been found that hydroxy-, acetoxy-, amino-, acetamido- and nitro- acetophenones all undergo the reaction.

Our recent demonstration[1a] that styrene undergoes the reaction with ammonium polysulfide induced us to attempt the application of the reaction to styrene and several of its substitution products under reflux conditions with morpholine.[9]

In the reaction of styrene with sulfur and morpholine a great many experiments were carried out in the search for optimal reaction conditions. The conclusions which we have been able to draw from these data are: (1) The time of refluxing usually employed has been much longer than is necessary, one to two hours being sufficient. (2) The best molar ratio of styrene: sulfur: morpholine is 1:2.5:2; when the ratio of styrene and morpholine is held constant and the amount of sulfur is cut to 2.25 the yield drops by about 5% and if it is cut to 2.0 the yield drops by about 10%, whereas use of more than 2.5 moles of sulfur does not increase the yield; the need for 2.5 moles of sulfur instead of the theoretical 2.0 moles is undoubtedly due to loss of hydrogen sulfide through the condenser during the refluxing period. (3) There is no relationship between the yield and the ratio sulfur/morpholine provided the actual amount of each is sufficient.

2-Chlorostyrene, 4-chlorostyrene, 4-chloroacetophenone and 2,5-dichlorostyrene were all converted to the corresponding phenylacetic acids by the same general procedure as was developed for the conversion of styrene to phenylacetic acid. A summary of the data on the reactions is given in Table I. The three isomeric hydroxyacetophenones offered no difficulty in their conversion to hydroxyphenylacetic acids. When *m*-acetoxyacetophenone was subjected to the reaction the ester linkage was broken and a good yield of *m*-hydroxyphenylthioacetmorpholide was obtained. The three isomeric methoxyacetophenones were similarly converted to the methoxyphenylacetic acids; the reactions with the *ortho*- and *meta*- isomers have been previously reported[5] but the yields were substantially lower than we were able to obtain.

The interesting observation was made that *p*-methoxyphenylthioacetmorpholide underwent almost complete cleavage of the methoxyl group to produce *p*-hydroxyphenylacetic acid when it was refluxed with 50% sulfuric acid. This cleavage was not observed with the *meta*- or *ortho*- isomers.

m- and *p*-aminoacetophenone underwent smooth conversion to the respective aminophenylacetic acids, just as did their acetyl derivatives. In the case of the latter the acetyl group remained intact during thiomorpholide formation. *o*-Acetamidoacetophenone similarly gave the expected acetamidothiomorpholide but this on acid hydrolysis gave oxindole.

When the reaction was applied to *m*-nitroacetophenone the nitrothiomorpholide was obtained but in only 30% crude yield. The other 70% of the material, which was acid-soluble, evidently was a compound in which the nitro group had undergone some reduction.

Further Extensions of the Reaction

When the object of a Willgerodt reaction has been a thioamide of an amine other than morpholine the reactant has been heated under pressure with sulfur and the amine: Kindler[4,6,7] used anhydrous ammonia, methylamine, dimethylamine, diethylamine, piperidine and β-naphthylamine, and Hartmann, Miescher, Kaegi and Bosshard[10] used methylamine, diethylamine, dipropylamine and piperidine. Although Schwenk and Bloch[5] stated in a footnote that piperidine was also used in some of their experiments, no data have been

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(1) For previous papers in this series see King and McMillan, THIS JOURNAL, **68**, (a) 525, (b) 632, (c) 1369 (1946).

(2) Presented before the Organic Division of the American Chemical Society at the Chicago meeting, Sept. 10, 1946.

(3) Willgerodt, *J. prakt. Chem.*, [2] **80**, 183 (1909).

(4) Kindler and Li, *Ber.*, **74**, 321 (1941).

(5) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

(6) (a) Kindler, *Ann.*, **431**, 187 (1923); (b) German Patent 405,675; (c) *Arch. pharm.*, **265**, 389 (1927).

(7) (a) Kindler and Peschke, *ibid.*, **270**, 340 (1932); (b) **272**, 236 (1934).

(8) One of the Referees and the Editor have kindly called our attention to the unpublished manuscript "Preparation of Hydroxyphenylalkanoic Acids by the Willgerodt Reaction" by Ott, Mattano and Coleman in which the authors have converted *o*-, *m*- and *p*-hydroxyacetophenone into the corresponding hydroxyphenylacetic acids and *p*-hydroxypropiophenone into β-(*p*-hydroxyphenyl)-propionic acid in 62, 41, 81 and 41% crude yields respectively by means of aqueous ammonium polysulfide in an agitated heated autoclave.

(9) The conversion of styrene to phenylthioacetmorpholide by sulfur and morpholine under reflux conditions has also been carried out in 51% yield by Carmack and DeTar, THIS JOURNAL, **68**, 2029 (1946).

(10) Hartmann, Miescher, Kaegi and Bosshard, Canada patent 414,941. See also British Patent 558,774.

TABLE I

Starting material, S or A[a]		Phenylthioacetmorpholide M. p., °C.[b]	Phenylthioacetmorpholide Formula	Analyses, % N Calcd.	Analyses, % N Found	Hydrolytic procedure	Yield, % of phenylacetic acid[c]	M. p., °C., of acid
	S	79–80	$C_{12}H_{15}NOS$	[d]		I[e]	84	76–77
2-Cl	S	115.5–116	$C_{12}H_{14}ClNOS$	5.48	5.39	I	63	94–95[f]
4-Cl	S	96–97	$C_{12}H_{14}ClNOS$	5.48	5.04	I	59	99–100[g]
4-Cl	A	96–97	$C_{12}H_{14}ClNOS$			I	28	99–100
2,5-Cl_2	S	135–136	$C_{12}H_{13}Cl_2NOS$	4.82	4.80	I	61	106.5–107
2-HO	A	160–161[h]	$C_{12}H_{15}NO_2S$	5.91	5.63	II[i]	59	138–141[j,k]
3-HO	A	97.5–98[h]	$C_{12}H_{15}NO_2S$	5.91	5.93	II	66	120–126[k,l]
4-HO	A	124.5–125.5	$C_{12}H_{15}NO_2S$	5.91	5.92	II	50	145–148[m]
3-AcO	A	97.5–98[h']						
2-CH_3O	A	64.5–65[n,o]	$C_{13}H_{17}NO_2S$	5.57	5.53	I	70	119.5–121.5[p]
3-CH_3O	A	[q]				I	82	68–69
4-CH_3O	A	68.5–69	$C_{13}H_{17}NO_2S$	5.57	5.53	I	36[r]	83–84[s]
3-H_2N	A	129–130	$C_{12}H_{16}N_2OS$	11.86	11.80	III[t]	61	144–146.5[u]
4-H_2N	A	77.5–79[v]	$C_{12}H_{16}N_2OS$	11.86	11.76	III	51[w]	196–197[x]
2-AcNH	A	161.5–162.5	$C_{14}H_{18}N_2O_2S$	10.07	9.45	III	[y]	
3-AcNH	A	158.5–159	$C_{14}H_{18}N_2O_2S$	10.07	10.08	III	68	144–146.5[u]
4-AcNH	A	132.5–133	$C_{14}H_{18}N_2O_2S$	10.07	10.08	III	70	196–197[x]
3-O_2N	A	138.5–139.5	$C_{12}H_{14}N_2O_3S$	10.52	10.89	I	7[y]	117–119[l,u]

[a] S is styrene, A is acetophenone. [b] After recrystallization from absolute alcohol unless otherwise noted. [c] Over-all yield of acid, based on the amount of olefin or ketone used. [d] Prepared from acetophenone and analyzed by Schwenk and Bloch.[5] [e] Several hours refluxing with 50% (by weight) sulfuric acid. [f] Mehner, *J. prakt. Chem.*, [2] **62**, 556 (1900). [g] v. Walther and Wetzlich, *ibid.*, [2] **61**, 195 (1900). [h] After recrystallization from toluene. [h'] *m*-Hydroxyphenylthioacetmorpholide, after recrystallization from toluene, obtained in 70% yield. [i] Several hours refluxing with 25% sodium hydroxide. [j] Stoermer, *Ann.*, **313**, 83 (1900). [k] M. p. of crude acid. [l] Salkowski, *Ber.*, **17**, 507 (1884). [m] *Ibid.*, **12**, 1438 (1879). [n] Reported as an oil by Schwenk and Bloch.[5] [o] After recrystallization from Skellysolve C. [p] Pschorr, Wolfes and Buckow, *Ber.*, **33**, 166 (1900). [q] This thioamide was not isolated, since Schwenk and Bloch[5] have already characterized it. [r] About 28% of *p*-hydroxyphenylacetic acid was also obtained; see Experimental part. [s] Cannizzaro, *Ann.*, **117**, 246 (1861). [t] Several hours refluxing with concentrated hydrochloric acid, [u] Gabriel and Borgmann, *Ber.*, **16**, 2065 (1883). [v] After recrystallization from toluene–Skellysolve C. [w] The yield of hydrochloride was 66%. [x] Bedson, *J. Chem. Soc.*, **37**, 92 (1880). [y] See Experimental Part.

published regarding the use of any amine other than morpholine, when the reaction is carried out under reflux conditions. We have made comparative studies on the use of ten amines in the reaction with styrene and sulfur under reflux conditions. The results are summarized in Table II. We are not in a position at the present time to account for the considerable variation in yield of product obtained from closely related amines.

TABLE II

Amine used	Thioamide M. p., °C.	Thioamide Formula	Analyses, % N Calcd.	Analyses, % N Found	Yield, % of phenylacetic acid[a]
Morpholine	79–80[b]				84
n-Heptylamine					59
Piperidine[c]	77.5–78.5[d]	$C_{13}H_{17}NS$	6.38	6.54	58
2-Ethylhexylamine					49
Cyclohexylamine	79–80[d]	$C_{14}H_{19}NS$	6.00	6.07	47
Benzylamine	85–85.5[d]	$C_{15}H_{15}NS$	5.80	5.94	34
Aniline	86.5–87.5[d]	$C_{14}H_{13}NS$	6.16	6.16	23
n-Butylamine					12.5
Diethanolamine					10.3
Monoethanolamine					3.5

[a] This is over-all yield of acid based on styrene. [b] Prepared and analyzed by Schwenk and Bloch.[5] [c] Schwenk and Bloch[5] reported that piperidine was also used in some of their experiments but no other information was given. [d] Crystallized from Skellysolve C.

A distinct advantage of the use of sulfur and an amine is that both substances can be separately weighed out or measured with ease; but the formation of thioamides instead of unsubstituted oxygen amides may occasionally be a disadvantage. Although we have recently shown[1c] that the preparation of ammonium polysulfide of constant composition is readily accomplished, the prepared material contains a fixed ratio of ammonia to sulfur which cannot be easily varied at will over more than a relatively narrow range. It would greatly simplify the preparation of carboxylic amides if there could be found some easy means of using as the reagent any predetermined ratio of ammonia to sulfur. Since Patrick[11] has claimed that when sulfur is heated with aqueous alkalies it goes into solution with formation of alkaline polysulfide, we have utilized this in the Willgerodt reaction.

Exploratory experiments were made with sulfur and aqueous ammonia on a variety of substances comprising ketones, alcohols, olefins and mercaptans of both the purely aliphatic and of the aromatic–aliphatic series. The compounds tested and the products obtained are given in Table III.

Through an entirely different approach Carmack and co-workers[12] have likewise recently concluded that the Willgerodt reaction can be satisfactorily carried out with free sulfur and

(11) Patrick, British Patent 354,310; *C. A.*, **26**, 3882 (1932).

(12) Carmack and co-workers, THIS JOURNAL, **68**, 2025, 2029, 2033 (1946).

TABLE III

Starting material	Acid amide obtained	Yield, % of amide[a]
Acetophenone	Phenylacetic	62
4-Methyl-2-pentanone	Isocaproic	20
Phenylmethylcarbinol	Phenylacetic	33
t-Butyl alcohol	Isobutyric	1
Styrene	Phenylacetic	61[b]
Decene-1	Decanoic	3
2-Phenethyl mercaptan	Phenylacetic	92
Decyl mercaptan	Decanoic	100

[a] No particular significance should be attached to the yields reported since the experiments were merely intended to show that the reaction would proceed and no attempt was made to find optimal conditions for any particular compound. [b] An additional 32% of phenylacetic acid was obtained; in no other case was the mixture worked up for the acid.

aqueous ammonia as the initial reagent and have used this procedure on several ketones, alcohols, olefins and acetylenes.

The sulfur–ammonia procedure has been used in the present work for the preparation of the two new amides 2,5-dichlorophenylacetamide and *m*-methoxyphenylacetamide.

Experimental[13,14]

All of the starting materials (styrenes and acetophenones) for the reactions described are commercially available unless otherwise noted. The commercial materials were used without further purification.

Phenylacetic Acid.—A mixture of styrene (104 g., 1.00 mole), sulfur (80 g., 2.50 moles) and morpholine (174 g., 2.00 moles) was refluxed two hours (internal temperature rising to about 175°). The cooled reaction mixture was taken up in chloroform (some sulfur remained undissolved) and the chloroform solution was washed successively with an equal volume of water, sufficient dilute hydrochloric acid to remove the excess morpholine, and finally with an equal volume of water. The solvent was removed under vacuum and the residue of crude phenylthioacetmorpholide was refluxed for ten hours with 1200 cc. of 50% (by weight) sulfuric acid. The cooled hydrolysis mixture was extracted with three 500-cc. portions of ether and the combined ethereal extract was washed with 600 cc. of 12% caustic soda. The caustic wash was acidified with concentrated hydrochloric acid and then extracted three times with 300-cc. portions of ether. Removal of the solvent from the combined ethereal extract gave 114 g. (84% yield) of nicely crystalline phenylacetic acid, m. p. 72–74°.

One run in which the original reaction mixture was concentrated under vacuum on the steam cone and then hydrolyzed directly with 50% sulfuric acid gave only a 59% yield of phenylacetic acid, m. p. 71–74°.

2,5-Dichlorophenylthioacetmorpholide.—After a mixture of 2,5-dichlorostyrene (43.3 g., 0.25 mole), sulfur (20 g., 0.625 mole) and morpholine (43.5 g., 0.50 mole) had been refluxed for two hours, taken up in chloroform and washed, removal of the solvent left a semi-crystalline residue which weighed 75 g. (109% of the theoretical amount; in nearly every case the weight of the crude thiomorpholide is greater than theoretical). A sample for analysis, after three recrystallizations from absolute alcohol, was white[15] and melted at 135–136°.

2,5-Dichlorophenylacetic Acid.—A portion of the above-described crude thiomorpholide (31.7 g., representing 0.106 mole of 2,5-dichlorostyrene) was refluxed for six hours with 300 cc. of 50% (by weight) sulfuric acid. Working up in the usual manner gave 12.5 g. (61% yield) of crystalline 2,5-dichlorophenylacetic acid. After two recrystallizations from water it melted at 106.5–107°.

Anal. Calcd. for $C_8H_6Cl_2O_2$: Cl, 34.63. Found: Cl, 35.05.

The same procedure was used for the conversion of 2-chlorostyrene, 4-chlorostyrene and 4-chloroacetophenone to the known 2- and 4-chlorophenylacetic acids.

2,5-Dichlorophenylacetamide.—2,5-Dichlorostyrene (17.3 g., 0.10 mole), sulfur (6.4 g., 0.20 mole) and ammonia (19.8 cc. of 28% ammonia, 0.30 mole) were heated four hours at 200° in a pressure tube. Filtration of the reaction mixture gave an 11% yield of 2,5-dichlorophenylacetamide, m. p. 156–157° after recrystallization from water.

Anal. Calcd. for $C_8H_7Cl_2NO$: N, 6.86. Found: N, 6.90.

The *o*-, *m*- and *p*-**hydroxyphenylthioacetmorpholides** were prepared in essentially the manner described for the dichlorophenyl derivative. They were hydrolyzed by two and one-half hours refluxing with 25% caustic soda. The crude thiomorpholide obtained from *p*-hydroxyacetophenone was also hydrolyzed by refluxing for six hours with 50% sulfuric acid to give a 45% yield of acid, as compared with a 50% yield obtained when 25% caustic soda was used for hydrolysis.

m-**Acetoxyacetophenone.**—Acetylation of the hydroxy ketone with acetic anhydride–potassium acetate in the usual manner gave the acetoxy derivative, b. p. 147° (9 mm.), m. p. 44–44.5°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.61. Found: C, 67.62; H, 5.42.

The three **methoxyacetophenones** were prepared from the corresponding hydroxy compounds by the usual procedure with methyl sulfate and alkali.

p-**Methoxyphenylacetic Acid.**—A mixture of *p*-methoxyacetophenone (37.5 g., 0.25 mole), sulfur (20 g., 0.625 mole) and morpholine (43.5 g., 0.50 mole) was refluxed for one hour. After the mixture was taken up in chloroform, washed in the usual manner, and the solvent removed, the residue was refluxed for eight hours with 300 cc. of 50% (by weight) sulfuric acid. The hydrolysis mixture was extracted three times with ether (200-cc. portions), the combined ethereal extract was washed with 250 cc. of 7% caustic soda, the alkaline wash was acidified and then extracted three times with ether. Removal of the solvent from the combined ethereal extract left 29.0 g. (70% yield, crude) of crystalline residue. Recrystallization of this material from 500 cc. of water gave 15 g. (36% yield) of *p*-methoxyphenylacetic acid, m. p. 83–84°. Concentration of the mother liquor to 25 cc. yielded 3.5 g. (9% yield) of *p*-hydroxyphenylacetic acid, m. p. 136–144°. Evaporation of this mother liquor to dryness gave 7.5 g. (about 19%) of a mixture of the two acids, m. p. 90–138°.

When a small amount of pure *p*-methoxyphenylthioacetmorpholide was refluxed for eight hours with 50% sulfuric acid the methoxyl group underwent almost complete cleavage, yielding *p*-hydroxyphenylacetic acid. This cleavage did not occur with the *m*-isomer and not noticeably with the *o*-isomer.

m-**Methoxyphenylacetamide.**—*m*-Methoxyacetophenone (3.00 g., 0.02 mole), sulfur (1.28 g., 0.04 mole) and ammonia (3.96 cc., 0.06 mole) were heated for four hours at 200°. Continuous benzene extraction of the reaction mixture for one hour removed the amide. Concentration of the extract, followed by dilution with Skellysolve A, gave 1.75 g. (53% yield) of crystalline amide which melted at 125–125.5° after recrystallization from water.

Anal. Calcd. for $C_9H_{11}NO_2$: N, 8.48. Found: N, 8.57.

Four hours at 195° gave a 56% yield, four hours at 174° a 65% yield and four hours at 215° gave no amide at all, although when the tube was heated to 215° and then

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(13) Melting points and boiling points are uncorrected.

(14) All analytical determinations were carried out under the direction of Mr. Morris E. Auerbach in the Analytical Laboratories of this Institute.

(15) Some of the thiomorpholides were obtained in the form of white crystals while others retained a yellow color after repeated recrystallization and charcoaling.

immediately allowed to cool there was obtained a 76% yield of amide.

***m*-Aminophenylacetic Acid.**—A mixture of *m*-aminoacetophenone (67.5 g., 0.50 mole), sulfur (40.0 g., 1.25 mole) and morpholine (87 g., 1.00 mole) was refluxed for two hours. The cooled reaction mixture was taken up in chloroform and the solution was washed twice with water. The chloroform was removed under vacuum and the residue was refluxed for four hours with 500 cc. of concentrated hydrochloric acid. Precipitated sulfur was removed by filtration and the filtrate was taken to dryness under vacuum. An excess of 35% caustic soda was added and the solution was again taken to dryness in order to remove retained morpholine. An excess of concentrated hydrochloric acid was added and the mixture was taken to dryness a third time, then the residue was leached with boiling absolute alcohol (300 cc.). The solvent was removed from this alcoholic extract and the residue was refluxed one-half hour with 500 cc. of concentrated hydrochloric acid (see following paragraph). The hydrochloric acid was removed under vacuum and the residue was dried by azeotropic distillation with toluene. The dry residue of *m*-aminophenylacetic acid hydrochloride weighed 88.5 g. (94.5% yield). A small portion of the material was recrystallized from absolute alcohol; its decomposition point, in the range of 200°, varied with the rate of heating.

Anal. Calcd. for $C_8H_9NO_2 \cdot HCl$: Cl (ionic), 18.93. Found: Cl (ionic), 18.84.

Unless the residue from the alcoholic leaching, mentioned above, is refluxed with hydrochloric acid the product is **ethyl *m*-aminophenylacetate hydrochloride**. For example, one run in which this hydrolysis was omitted gave an 85% yield of the ester hydrochloride which melted, after recrystallization from ethanol–ether, at 126–127°.

Anal. Calcd. for $C_{10}H_{13}NO_2 \cdot HCl$: Cl (ionic), 16.46; neut. equiv., 215.5. Found: Cl (ionic), 16.23; neut. equiv., 217.

The crude amino acid hydrochloride (83.5 g.) was treated with one equivalent of sodium hydroxide in 500 cc. of water. After decolorization there was obtained from the chilled solution 41 g. (61% yield) (based on the amount of ketone used) of *m*-aminophenylacetic acid, m. p. 144–146.5°.

When equimolar amounts of *m*-aminoacetophenone, sulfur and morpholine were refluxed for eight hours, then poured into water and the product extracted with ether there was obtained a 38% yield of *m*-aminophenylthioacetmorpholide which melted at 130–130.5° after two recrystallizations from ethanol.

***p*-Aminophenylacetic Acid.**—This was prepared and hydrolyzed in the same manner as the *m*-isomer. By a fortuitous circumstance the hydrolysis mixture was chilled and a 66% yield of *p*-aminophenylacetic acid hydrochloride was removed by filtration. A small portion of this material was recrystallized first from water and then from alcohol; its decomposition point, in the range 215 to 240°, varied with the rate of heating.

Anal. Calcd. for $C_8H_9NO_2 \cdot HCl$: Cl (ionic), 18.93. Found: Cl (ionic), 18.64.

The rest of the material (61 g.) was treated with one equivalent of sodium hydroxide and sufficient water for complete solution at the boiling point (1500 cc. required). After decolorization there was obtained a 50.5% yield (based on *p*-aminoacetophenone) of *p*-aminophenylacetic acid, m. p. 196–197°.

***m*-Acetamidophenylthioacetmorpholide and *p*-Acetamidophenylthioacetmorpholide.**—*m*-Acetamidoacetophenone,[16] m. p. 126–127°, and *p*-acetamidoacetophenone,[17] m. p. 168–169°, each prepared in the usual manner from the free amino ketones, were converted to the expected acetamidophenylthioacetmorpholides by the same procedure as was used for the unacetylated compounds. Hydrochloric acid hydrolysis gave the aminophenylacetic acids.

***o*-Aminoacetophenone.**—*o*-Nitroethylbenzene (b. p. 133–135° under 37 mm., prepared in 37% yield by the procedure of Cline and Reid[18]) could not be oxidized to *o*-nitroacetophenone by air in the presence of chromic oxide–calcium carbonate catalyst according to the procedure of Emerson and co-workers[19] for the oxidation of ethylbenzene to acetophenone; runs of varying length of time at various temperatures (up to 210°) gave complete recovery of starting material. Neither could it be converted directly to *o*-aminoacetophenone by heating with alcoholic caustic by the method Preuss and Binz[20] used for the conversion of *o*-nitrotoluene to anthranilic acid; the only identifiable product was a 16% yield of *o*-aminoethylbenzene, identified as its acetyl derivative,[21] m. p. 110.5–112°.

The desired amino ketone was eventually prepared by the procedure of Morgan and Moss[22] by nitration of acetophenone and reduction of the nitroketone; the pure *o*-aminoketone, b. p. 145–152° (30 mm.), was obtained in 17% yield, based on acetophenone. Acetylation in the usual manner gave *o*-acetamidoacetophenone,[23] m. p. 74–76°.

***o*-Acetamidophenylthioacetmorpholide.**—A mixture of *o*-acetamidoacetophenone (3.54 g., 0.02 mole), sulfur (1.60 g., 0.05 mole) and morpholine (3.48 g., 0.04 mole) was refluxed for one hour. On being worked up in the usual manner the reaction mixture yielded the expected thioamide in 75% yield; m. p. 161.5–162.5°, after three recrystallizations from absolute alcohol.

Oxindole.—The same reaction was repeated and the crude thioamide was refluxed for three hours with concentrated hydrochloric acid (50 cc.). The hydrolysis mixture was chilled and extracted twice with 50-cc. portions of ether. Removal of the solvent from the combined extract gave a crystalline solid (about 0.3 g.) which melted at 122–123° after recrystallization from water. Reissert[24] reported the m. p. of purified oxindole as 126°.

Willgerodt Reaction on *m*-Nitroacetophenone.—A mixture of *m*-nitroacetophenone (16.5 g., 0.10 mole, m. p. 76–78°, prepared in 67% yield by nitration of acetophenone according to the procedure of Morgan and Watson[25]), sulfur (8.0 g., 0.25 mole) and morpholine (17.4 g., 0.20 mole) was refluxed for one hour. The cooled reaction mixture was taken up in chloroform and washed successively with water, dilute hydrochloric acid, and water. Removal of the chloroform left 8.0 g. (30% crude yield) of a semicrystalline residue. After four recrystallizations from absolute alcohol the *m*-nitrophenylthioacetmorpholide melted at 138.5–139.5°.

The hydrochloric acid wash of the original chloroform extract was made alkaline and extracted with chloroform. Removal of the chloroform from the extract left 18 g. (70% crude yield) of crystalline solid which melted at 159–160° after four recrystallizations from absolute alcohol.

Anal. Calcd. for $C_{12}H_{16}N_2O_2S$: N, 11.11; S, 12.71; mol. wt., 252. Found: N, 11.13; S, 13.07; mol. wt. (in benzene by freezing point), 227.

A little of the material was suspended in acetic anhydride, a drop of sulfuric acid was added, and the material went into solution with evolution of heat. The mixture was immediately poured on ice and stirred until all acetic anhydride was decomposed. The solid product was removed by filtration and, after recrystallization from absolute alcohol, melted at 196–197° and analyzed satisfactorily for a mono-acetyl derivative.

Anal. Calcd. for $C_{14}H_{18}N_2O_3S$: N, 9.54. Found: N, 9.67.

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[16] Rupe, Braun and von Zembruski, *Ber.*, **34**, 3523 (1901).

[17] Kunckell, *ibid.*, **33**, 2641 (1900).

[18] Cline and Reid, THIS JOURNAL, **49**, 3150 (1927).

[19] Emerson, Heyd, Lucas, Chapin, Owens and Shortridge, *ibid.*, **68**, 674 (1946).

[20] Preuss and Binz, *Z. angew. Chem.*, **13**, 385 (1900); see also German Patent 114,839 and Scholl, *Monatsh.*, **34**, 1011 (1913).

[21] Paucksch, *Ber.*, **17**, 768 (1884).

[22] Morgan and Moss, *J. Soc. Chem. Ind.*, **42**, 461T (1923).

[23] Gevekoht, *Ber.*, **15**, 2086 (1882).

[24] Reissert, *ibid.*, **41**, 3926 (1908).

[25] Morgan and Watson, *J. Soc. Chem. Ind.*, **55**, 29T (1936).

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.

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

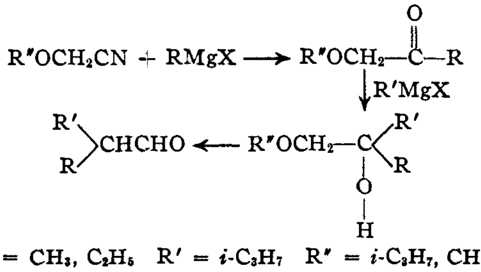
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY, AND THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

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]

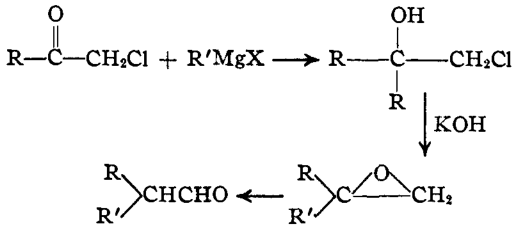
The first method investigated in this work was similar to that originally employed by Béhal and Sommelet[7] and by Stoermer[8] for the preparation of some dialkylacetaldehydes. In this method, the alkyl ether of a substituted ethylene glycol was heated with dilute acids or with anhydrous oxalic acid.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



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

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).