

for  $\text{C}_{10}\text{H}_{16}\text{O}_4$ : C, 59.98; H, 8.05; saponification equiv., 200. Found: C, 59.17; H, 7.69; saponification equiv., 200. There was 18 g. of higher boiling material, b. p. 134–185° (4 mm.) which was not characterized and 16 g. of residue. The crude carbonate fraction was refractionated to give 12 g. of ethyl carbonate, b. p. 121–123°;  $n_D^{20}$  1.3817.

*trans*- $\alpha$ -Methylglutaconic Acid.—A mixture of 6 g. of the glutaconate (II) and 55 ml. of aqueous 10% hydrochloric acid was refluxed until solution was complete. The hydrochloric acid and water were removed under reduced pressure and the remaining solid recrystallized from water to give the acid, m. p. 145°. <sup>12</sup> *Anal.* Calcd. for  $\text{C}_6\text{H}_8\text{O}_4$ : C, 50.00; H, 5.60. Found: C, 49.78; H, 5.62.

A semi-anilide was prepared according to the method of Thorpe and Thole<sup>13</sup> which after recrystallization from ethyl acetate melted at 189–190° and decomposed with gas evolution when held slightly above the melting point.<sup>13</sup>

(12) Thorpe and Wood, *J. Chem. Soc.*, **103**, 1757 (1913), report m. p. 145–146°. See ref. 4 for establishment of configuration.

(13) Thorpe and Thole, *ibid.*, **99**, 2231 (1911).

mm.)–63° (1 mm.),  $n_D^{20}$  1.4157; 10 g. of an intermediate cut, b. p. 63–123° (1 mm.),  $n_D^{20}$  1.4423; 17 g. (19%) of crude glutarate (III), b. p. 123–140° (1 mm.),  $n_D^{20}$  1.4460; 4 g. of higher boiling material, b. p. 140–160° (1 mm.),  $n_D^{20}$  1.4653; and 5 g. of residue. Refractionation of crude III gave the pure glutarate, b. p. 125° (1 mm.);  $n_D^{20}$  1.4400; saponification equiv., 122 (calcd. 123).

**Ethyl 4-Hydroxy-5-methylisophthalate (V).**—To 33.5 g. (0.5 mole) of dry powdered sodium ethoxide there was added, with stirring, 280 ml. of anhydrous ether, 87 g. (0.5 mole) of ethyl methylmalonate and 144 g. (1 mole) of the acrylate (I). With continued stirring the bulk of the ether was removed by fractionation and 200 g. of dry toluene was added. Continued fractionation gave 88 g. of an ethanol-toluene mixture. To the cooled reaction mixture was added 80 g. of aqueous 37% acetic acid, the oil layer separated, washed with 50 ml. of water and dried over anhydrous sodium sulfate. Fractionation gave 219 g. of a mixture consisting of ethanol, toluene and ethyl carbonate, b. p. 77° (755 mm.)–35° (1 mm.); 30.5 g. of recovered acrylate (I) and ethyl methylmalonate, b. p. 38–52° (1 mm.); 9 g. of an intermediate cut, b. p. 58–

**Ethyl  $\alpha$ -Methyl- $\beta$ -ethoxyglutarate (III).**—In a similar experiment there was mixed 0.16 mole of the quaternary base containing an equivalent of ethanol, 0.37 mole of ethyl methylmalonate and 0.54 mole of the acrylate (I). After stirring at 40–45° for nine hours, the cooled mixture was neutralized with 50 g. of aqueous 20% acetic acid, washed with 50 ml. of water and dried over anhyd. sodium sulfate. Fractionation gave 11 g. of ethanol, b. p. 75–79°; 5 g. of ethyl carbonate, b. p. 30–33° (4 mm.),  $n_D^{20}$  1.3857; 95 g. of a mixture consisting of ethyl methylmalonate and the acrylate (I), b. p. 51° (14

164° (4 mm.); and 59 g. (47%) of crude ester (V), b. p. 167–174° (4 mm.) which solidified on standing, m. p. 53–55°. There was 18 g. of a higher boiling material, b. p. to 254° (4 mm.) and 7 g. of residue.

The first fraction was refractionated to give 13 g. of ethyl carbonate, b. p. 125°. The solidified ester (V) fraction was recrystallized from ethanol, m. p. 61–62°.<sup>6</sup>

*Anal.* Calcd. for  $C_{13}H_{18}O_5$ : C, 61.89; H, 6.39; molecular weight, 252. Found: C, 61.67; H, 6.36; molecular weight, 251.

The high boiling fraction (b. p. to 254° (4 mm.)) solidified on standing and was recrystallized from ethanol to give ethyl trimesate, m. p. 132–135°, which did not depress the m. p. of an authentic sample.

**4-Hydroxy-5-methylisophthalic Acid (VI).**—The ester (V) (4 g.) was refluxed for one hour with a solution consisting of 3 g. of potassium hydroxide dissolved in 30 g. of an ethanol–water (1:1) mixture. The cooled mixture was acidified with dilute hydrochloric acid, the solid material removed on a filter and recrystallized from ethanol, m. p. 277.5–278°.<sup>7</sup>

**Ethyl Hydroxytrimesate (XV).**—To a suspension of 0.26 mole of sodium ethoxide in 200 ml. of ether was added 80 g. (0.5 mole) of ethyl malonate and 184 g. (1.28 moles) of the acrylate (I). The mixture was stirred and refluxed for eight hours. After cooling to 25° there was added 100 g. of aqueous 30% acetic acid, the organic layer separated and dried over sodium sulfate. Distillation through a short packed column gave, after removal of ether and ethanol, 177 g. of unreacted ethyl malonate and acrylate (I), b. p. 44–63° (1 mm.); 24 g. of an intermediate fraction, b. p. 63–210° (1–6 mm.); and 22 g. (14%) of crude XV, b. p. 212–220° (6 mm.) which crystallized on standing. The crude ester (XV), m. p. 67–72°, was recrystallized three times from ethanol to give pure XV, m. p. 86–87°.<sup>9</sup> Material prepared from other runs melted at 84–85.5°.

*Anal.* Calcd. for  $C_{15}H_{18}O_7$ : C, 58.05; H, 5.84; saponification equiv., 103.5. Found: C, 57.74; H, 6.14; saponification equiv., 105.

In another experiment a mixture of benzyltrimethylammonium ethoxide containing an equivalent of ethanol (0.5 mole), ethyl malonate (1 mole) and the acrylate (1.5 moles) was stirred three hours at room temperature and then nine hours at 40–43°. After neutralization there was obtained on fractionation 42 g. of ethanol, b. p. 75–78°; 18 g. of an intermediate cut, b. p. 25–90 (22 mm.); 249 g. of recovered malonate and acrylate (I), b. p. 62–68° (3 mm.); 4.5 g. of another intermediate fraction, b. p. 73–200° (6 mm.); and 32 g. of material, b. p. 200–215° (6 mm.) which solidified. Repeated crystallizations of the solid yielded a major fraction which was ethyl trimesate (IX), m. p. 132°. There was no depression in m. p. when mixed with an authentic sample of IX. The mother liquors from above yielded no constant melting material, melting range 97–129°. Repeating the above experiment and using 0.55 mole of malonate, 1.1 moles of acrylate (I) and 0.5 mole of the quaternary base gave 11 g. of ethyl carbonate, b. p. 125–127° and 45 g. of ethyl trimesate (IX), m. p. 133–135°.

**Hydroxytrimesic Acid (XVI).**—A mixture of 2 g. of the ester (XV) was refluxed for one hour with a solution of 2 g. of potassium hydroxide dissolved in 20 ml. of aqueous ethanol (1:1). Acidification produced the acid (XVI) which was collected on the filter and recrystallized from water. No true melting point could be obtained. Complete melting occurred at 298–300° but evidence of decomposition was observed before this point was reached. Ost<sup>9</sup> reports the acid (XVI) to decompose at 180° yielding carbon dioxide, phenol, salicylic acid and 4-hydroxyisophthalic acid. The latter acid is reported by Graebe and Kraft<sup>14</sup> to melt at 310°. Ullmann and Brittner<sup>15</sup> report hydroxytrimesic acid (XVI) as melting at 312°. It is probable that the latter authors have converted XV to

4-hydroxyisophthalic acid during their melting point determination.

*Anal.* Calcd. for  $C_9H_8O_7$ : C, 47.80; H, 2.67. Found: C, 47.69; H, 2.77.

**Ethyl Trimesate (IX).**—To 0.5 mole of benzyltrimethylammonium ethoxide containing an equivalent of ethanol was added with stirring and cooling 0.5 mole of the acrylate (I). After the exothermic reaction subsided, the mixture was heated to 45° and with continued stirring there was removed under reduced pressure through a short fractionation column 50 g. of a distillate which was collected in a dry ice–acetone trap and consisted essentially of ethanol. To the cooled reaction mixture was added 130 g. of aqueous 24% acetic acid whereupon a solid separated which was removed on the filter [36 g. of crude ester (IX)]. The crude ester (IX) was recrystallized from ethanol to give 21 g. of pure IX, m. p. 135–136°. From the alcoholic mother liquor an additional 5 g. of IX was obtained. The original mother liquor from neutralization yielded 7 g. of material. The total yield was 33 g. (67.5%). There was no depression in m. p. when mixed with an authentic sample.

**Ethyl 4-Hydroxy-5-formylisophthalate (XII).**—To 0.5 mole of powdered sodium ethoxide was added with stirring 350 ml. of anhydrous ether and 72 g. (0.5 mole) of the acrylate (I). The mixture was refluxed for five hours, 250 g. of dry toluene added and the ether removed by fractionation. An additional 250 g. of dry toluene was added and the fractionation continued over an eight-hour period to give 20 g. of an ethanol–toluene azeotrope b. p. 76° (68% ethanol by hydroxyl determination). To the cooled mixture was added 130 g. of aqueous 23% acetic acid, the oil layer separated, washed with water and dried over anhydrous sodium sulfate. Fractionation gave, after removal of toluene, 12.5 g. of unreacted acrylate (I) and ethyl  $\beta,\beta$ -diethoxypropionate, b. p. 52–70° (1 mm.); 9.5 g. of material, b. p. 70–140° (1 mm.); and 20.5 g. (48%) of the ester (XII), b. p. 167–169 (1 mm.). The last two fractions solidified. The solidified material, b. p. 70–140° (1 mm.), after several recrystallizations from ethanol was identified as  $\beta$ -ethoxyacrylic acid, m. p. 107–108° (no depression in melting point with an authentic sample).

*Anal.* Calcd. for  $C_9H_8O_3$ : C, 51.71; H, 6.94; molecular weight, 116. Found: C, 51.86; H, 6.90; molecular weight, 119.

The ester (XII) fraction was recrystallized from ethanol m. p. 111–112°. *Anal.* Calcd. for  $C_{13}H_{14}O_6$ : C, 58.64; H, 5.29; molecular weight, 265. Found: C, 58.96; H, 5.60; molecular weight, 263.

**4-Hydroxy-5-formylisophthalic Acid (XIII).**—To 1 g. of the ester (XII) was added 50 ml. of an aqueous 4% potassium hydroxide solution. After refluxing one hour, the mixture was cooled, neutralized with dilute hydrochloric acid and the solid removed on the filter. Recrystallization of the crude acid gave the pure acid, m. p. 260°, with gas evolution.<sup>11</sup>

## Summary

1. Ethyl methylmalonate and ethyl  $\beta$ -ethoxyacrylate (I) in the presence of benzyltrimethylammonium ethoxide gives ethyl  $\alpha$ -methyl- $\beta$ -glutaconate (II) and ethyl  $\alpha$ -methyl- $\beta$ -ethoxyglutarate (III). In the presence of sodium ethoxide these reactants produce ethyl 4-hydroxy-5-methylisophthalate (V).

2. Ethyl malonate and the acrylate (I) with sodium ethoxide yield ethyl hydroxytrimesate (XV). The quaternary ammonium base when used in place of sodium ethoxide gave ethyl trimesate (IX).

3. The acrylate (I) and the quaternary am-

(14) Graebe and Kraft, *Ber.*, **39**, 798 (1906).

(15) Ullmann and Brittner, *ibid.*, **42**, 2543 (1909).

monium base gave ethyl trimesate (IX) whereas sodium ethoxide and (I) yielded ethyl 4-hydroxy-5-formylisophthalate (XIII).

4. Mechanisms are postulated for these transformations.

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RECEIVED AUGUST 29, 1949

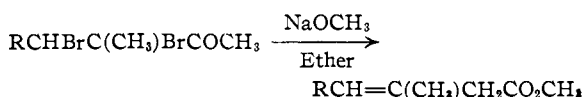
[CONTRIBUTION FROM THE WHITMORE LABORATORIES, THE SCHOOL OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE COLLEGE]

## The Rearrangement of $\alpha, \alpha'$ -Dibromoketones<sup>1</sup>

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The conversion of an  $\alpha, \alpha'$ -dibromo- $\alpha$ -alkylketone to an unsaturated acid was first reported by Favorskii, who found that 1,3-dibromo-3-methyl-2-butanone, on treatment with alcoholic potassium hydroxide, gave  $\beta, \beta$ -dimethylacrylic acid in 60% yield.<sup>2</sup> This reaction has also been carried out with steroidal compounds, 17,21-dibromopregnan-3( $\beta$ )-ol-20-one being converted to 17-pregnen-3( $\beta$ )-ol-21-oic acid.<sup>3</sup>

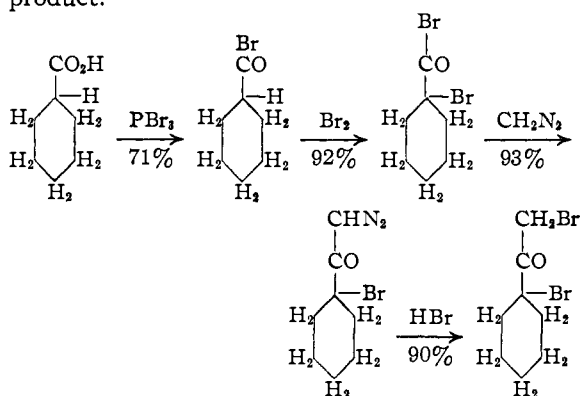
A closely related rearrangement of  $\alpha, \beta$ -dibromoketones to unsaturated esters has been observed in the pregnane series,<sup>4</sup> and has recently been extended to aliphatic compounds.<sup>5</sup> In this later work, it has been shown that  $\alpha, \beta$ -dibromo- $\alpha$ -alkylketones, on treatment with sodium methylate, yield  $\beta, \gamma$ -unsaturated esters.



The purpose of the present work was to extend the Favorskii rearrangement beyond the first member of the series in order to test its generality, and to determine the extent and nature of secondary reactions, if any. Furthermore, an effort was made to obtain an insight into any common basis for these two similar rearrangements. Four  $\alpha, \alpha'$ -dibromoketones, namely, 1,3-dibromo-3-methyl-2-butanone, 1,3-dibromo-3-methyl-2-pentanone, 1-(bromoacetyl)-1-bromocyclohexane and 2,4-dibromo-2,5-dimethyl-3-hexanone have been prepared and subjected to the same basic conditions which were employed in the  $\alpha, \beta$ -dibromoketone reactions. Since direct correlation of the two rearrangements was desired, three of these  $\alpha, \alpha'$ -dibromoketones have the same carbon skeleton as the compounds in the previously studied  $\alpha, \beta$ -dibromoketone series. Thus, the two groups of compounds differ only in the position of one of the bromine atoms.

These  $\alpha, \alpha'$ -dibromoketones were prepared by direct bromination of the ketones (Table I). Since this method of formation is not entirely free of

complications, one of the dibromoketones was prepared by the following series of reactions, which leaves little doubt as to the structure of the product.



The compounds prepared by the two methods were identical in all respects, and this indicates that the direct dibromination proceeds as expected, *viz.*:  $\text{RR}'\text{CHCOCH}_3 \xrightarrow{2\text{Br}_2} \text{RR}'\text{CBrCOCH}_2\text{Br}$ .

The products formed when these dibromoketones were treated with sodium methylate in anhydrous ether, in every case, consisted solely of the methyl ester of an  $\alpha, \beta$ -unsaturated acid. The nature of these esters and their properties are indicated in Table II. In all these reactions, heavy resins remained after the isolation of the methyl esters.

Comparing the results of these reactions with those from the  $\alpha, \beta$ -dibromoketone series, it is seen that the esters obtained from either type of ketone possess the same carbon skeleton. In every case, however,  $\alpha, \alpha'$ -dibromoketones give rise to  $\alpha, \beta$ -unsaturated esters, and  $\alpha, \beta$ -dibromoketones to esters with  $\beta, \gamma$ -unsaturation. One further difference in the two rearrangements which might be noted is the fact that both geometrical isomers of 3-methyl-2-pentenoic ester were obtained in the present work, whereas only one of the isomers of the 3-methyl-3-pentenoic acid was obtained from the corresponding  $\alpha, \beta$ -dibromoketone. That the reaction actually involves a carbon skeleton rearrangement at least in the case of  $\alpha, \alpha'$ -dibromoketones is indicated by the formation of the isopropylideneacetic ester from dibromoisopropylisobutyl ketone.

(1) Presented at the Organic Division of the St. Louis Meeting of the American Chemical Society, September 6, 1948.

(2) Favorskii, *J. prakt. Chem.*, [2] **88**, 658 (1913).

(3) Marker, Crooks and Wagner, *THIS JOURNAL*, **64**, 213, 817 (1942).

(4) Marker, Wagner and Wittbecker, *ibid.*, **64**, 2093 (1942).

(5) Wagner, *ibid.*, **71**, 3214 (1949).