[CONTRIBUTION FROM ROHM & HAAS COMPANY]

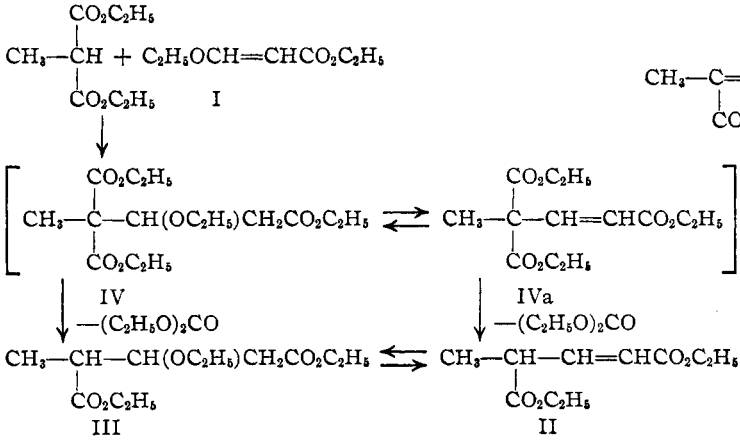
Michael Condensations with Ethyl β-Ethoxyacrylate[1]

BY W. J. CROXALL AND MARIAN F. FEGLEY

It seemed of interest to determine whether ethyl β-ethoxyacrylate (I)[2] would function as an acceptor in the Michael condensation.[3] This paper describes various condensations of the above type which have been carried out with this ester (I).

The condensation of ethyl methylmalonate with the acrylate (I) in the presence of benzyltrimethylammonium ethoxide gave ethyl carbonate, ethyl α-methyl-β-glutaconate (II) and ethyl α-methyl-β-ethoxyglutarate (III). The isolated glutaconate (II) appears to be the *trans* ester since saponification gave the known *trans* acid.[4] The course of this condensation is thought to occur as shown by the formulas.

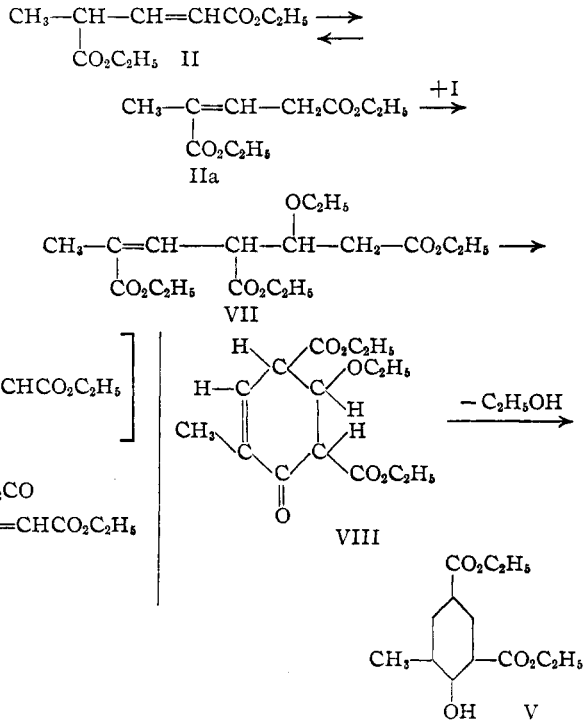
When the mole ratio of malonate, acrylate (I) and quaternary base is 1:2:1, the glutaconate (II) is isolated. On the other hand, when the ratio is 2:3:1, the glutarate (III) is formed. To account for these products it is assumed that the initial condensation produces the adducts IV and IVa. Alcoholysis of IVa then yields ethyl carbonate and the glutaconate (II).[5] The glutarate (III)



may be accounted for by a similar mechanism from the adduct IV or as indicated in the equations by addition of ethanol to the glutaconate (III). Actually in the experiment in which the glutaconate (II) was isolated a two-fold excess of acrylate (I) was present. This suggests that the acrylate (I) functions as an alcohol acceptor to form ethyl β,β-diethoxypropionate and accordingly favors the products on the right-hand side of the above equation, namely, the glutaconate (II).[2]

Attempts to use sodium ethoxide under identical experimental conditions in place of the quaternary ammonium condensation agent in the above condensation gave none of the esters II and III. However, this agent under forcing conditions yielded ethyl carbonate and ethyl 4-hydroxy-5-methylisophthalate (V)[6] as the main products. A small amount of ethyl trimesate (IX) was also isolated. The isophthalate (V) was further characterized by saponification to 4-hydroxy-5-methylisophthalic acid (VI).[7]

The formation of the isophthalate (V) may be accounted for as shown



In this mechanism the glutaconate[8] (II) is equilibrated to the isomeric glutaconate (IIa). Condensation of IIa with the acrylate (I) gives an intermediate (VII) which then undergoes a Dieckmann cyclization to produce the cyclic ketone (VIII). The ketone (VIII) in turn simultaneously loses one molecule of ethanol and enolizes to yield the isophthalate (V). It is possible

(1) For the previous paper of this series, see Croxall and Van Hook, THIS JOURNAL, **72**, 803 (1950).

(2) Croxall and Schneider, *ibid.*, **73**, 1257 (1949).

(3) Connor and McClellan, *J. Org. Chem.*, **3**, 570 (1939), have reviewed the structural requirements for various acceptor molecules in the Michael condensation. There does not appear to be any record of an alpha, beta unsaturated ester possessing a beta alkoxy having been used for this type condensation.

(4) Fitzgerald and Kon, *J. Chem. Soc.*, 725 (1937).

(5) Gidvoni, Kon and Wright, *J. Chem. Soc.*, 1027 (1932), have demonstrated that carbethoxyglutaconates of this type undergo alcoholysis to give alkyl carbonates and the corresponding glutaconates. See also ref. 11 and 12 for additional examples.

(6) Anschutz and Robitsek, *Ann.*, **346**, 358 (1906).

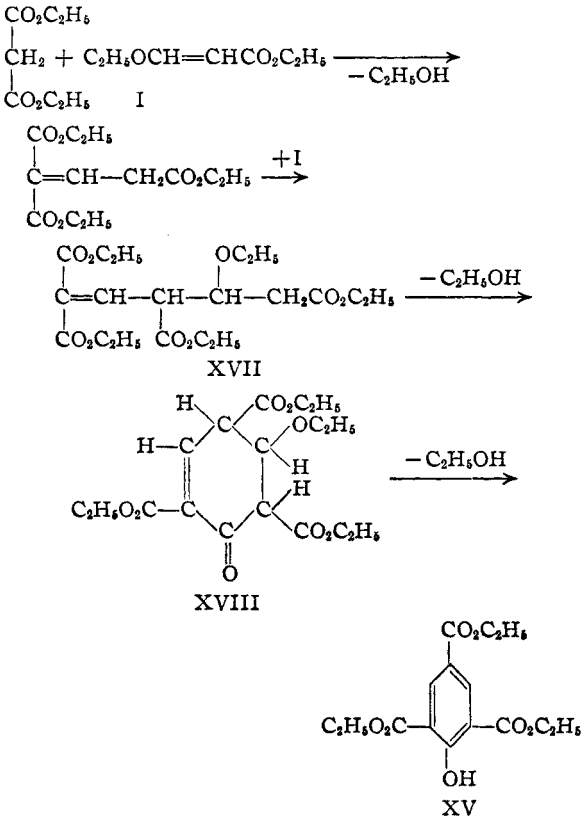
(7) Bottinger, *Ber.*, **13**, 1935 (1880).

(8) An alternate route would be the condensation of the glutarate (III) with the acrylate (I) to produce CH_3—$CH(CO_2C_2H_5)$—$CH(OC_2H_5)$—$CH(CO_2C_2H_5)$—$CH(OC_2H_5)$—$CH_2CO_2C_2H_5$.

of course that condensation of the adduct (IV) with the acrylate (I) could produce a tetracarboxy intermediate and that this intermediate *via* a Dieckmann cyclization would produce a cyclic beta keto ester. A reverse Claisen condensation on this keto ester, subsequent loss of ethanol and enolization would yield ethyl carbonate and the isophthalate (V).

Ethyl malonate, the acrylate (I) and sodium ethoxide gave a high boiling oil that solidified and from which ethyl hydroxytrimesate (XV)[9] was isolated The yields for this condensation were poor. The hydroxytrimesate (XV) gave hydroxytrimesic acid (XVI)[9] upon saponification.

The formation of the hydroxytrimesate (XV) is thought to proceed through an intermediate (XVII) which by a Dieckmann condensation gives a cyclic ketone (XVIII) and then yields the hydroxytrimesate (XV) as indicated in the equations



When benzyltrimethylammonium ethoxide was used in place of sodium ethoxide the major product was ethyl trimesate (IX) and no pure XV could be isolated. In some of these experiments ethyl carbonate was isolated indicating the presence of ethyl β-ethoxyglutarate and ethyl glutaconate. However, these compounds were not isolated nor were any final condensation products which could be derived from these materials, such as ethyl 4-hydroxyisophthalate, found.

In view of the above results it was thought to be of interest to examine the action of the condensation agents on the acrylate (I) alone. Benzyltrimethylammonium ethoxide and the acrylate (I) gave, in good yields, ethyl trimesate (IX). Reaction in this case occurred at mild temperatures. It is thought that initially the acrylate (I) by addition of ethanol produces ethyl β,β-diethoxypropionate. Condensation of the propionate and I first yields a dimer which through loss of ethanol produces an unsaturated dimer (Xa). Condensation of Xa with another molecule of I gives the trimers (Xb ⇄ X). Loss of ethanol from X produces the unsaturated trimer (XI) which then undergoes an internal Michael condensation. Subsequent loss of ethanol gives the trimesate (IX).

In the case of sodium ethoxide and the acrylate (I) there was obtained ethyl 4-hydroxy-5-formylisophthalate (XII) which was characterized by conversion to the known 4-hydroxy-5-formylisophthalic acid (XIII) by saponification.[10] Forcing conditions were necessary to obtain the isophthalate (XII). The initial steps for the formation of this ester (XII) are assumed to proceed through the saturated trimer (X) stage. However, to account for this ester (XII) it seems evident that a Dieckmann condensation must occur with subsequent enolization and loss of ethanol to give an acetal derivative (XIV) of the isophthalate (XII) which under the acid conditions used for neutralization produces the formyl ester (XII).

Acknowledgment.—The analyses were carried out under the direction of Dr. E. L. Stanley and Mr. C. W. Nash. Miss R. Lookabaugh performed some of the experiments. We wish to thank the Referee and Dr. R. Connor, both of whom suggested the more plausible mechanism used throughout this paper. Our original mechanism was that listed in ref. 8.

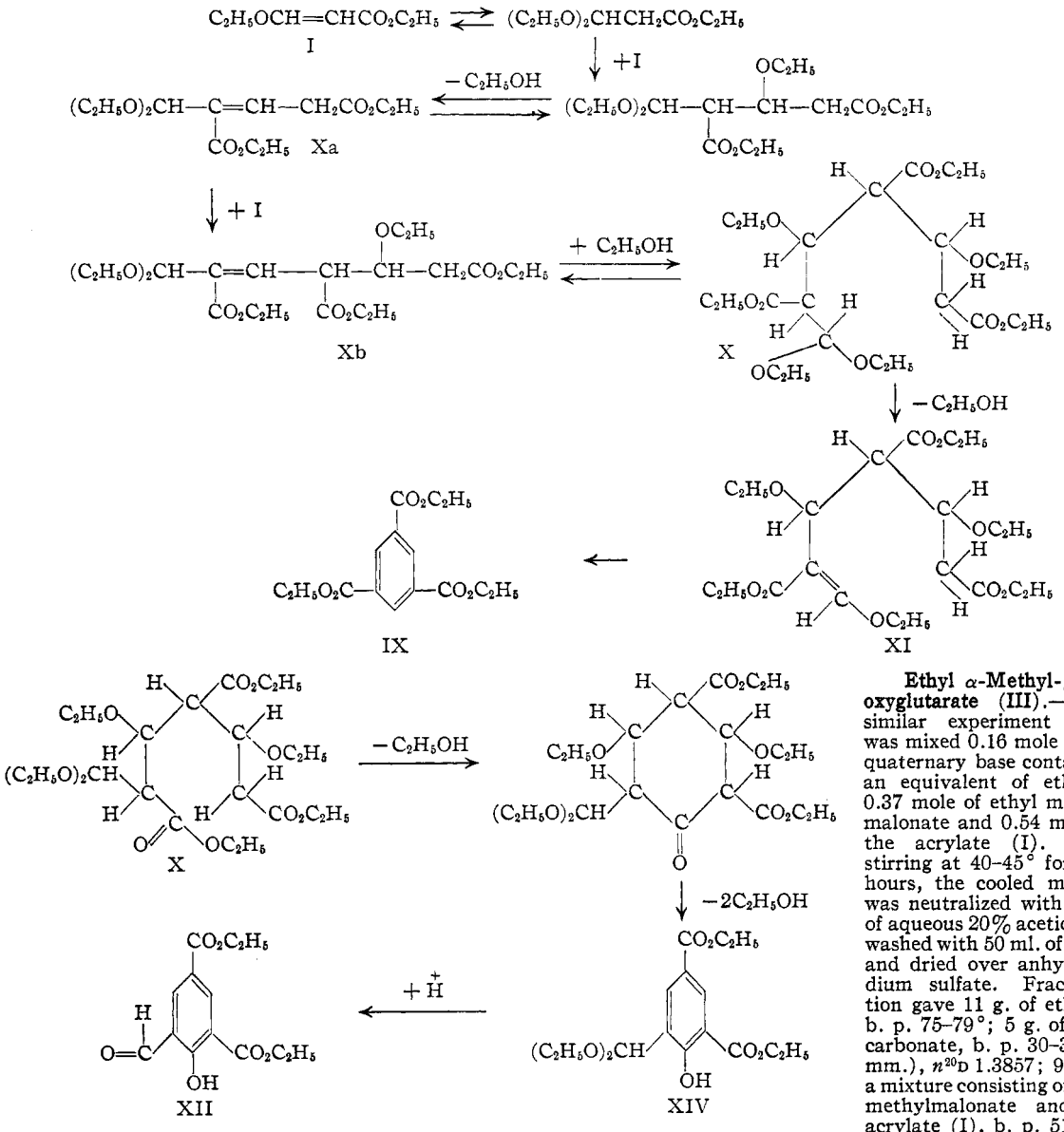
Experimental

Ethyl α-Methyl-β-glutaconate (II).—There was prepared as previously described[1] 0.98 mole of benzyltrimethylammonium ethoxide containing an equivalent of ethanol. To the ethoxide there was added with stirring and cooling, 171 g. (0.98 mole) of ethyl methylmalonate and then 288 g. (2.0 moles) of ethyl β-ethoxyacrylate (I). During the addition of the acrylate, the temperature rose from 27–41° and then started to fall fifteen minutes later. With continued stirring, the mixture was heated to 45° and held for four hours after which it was cooled, neutralized with 260 g. of aqueous 23% acetic acid, washed with 100 ml. of water, the organic layer separated and dried over anhyd. sodium sulfate. Fractionation gave 60 g. of ethanol–ethyl carbonate, b. p. 78–117°; 22 g. of crude ethyl carbonate, b. p. 30–50° (18 mm.); 321 g. of unreacted acrylate (I) and ethyl methylmalonate, b. p. 50° (18 mm.)–97° (14 mm.); 19.5 g. of an intermediate fraction, b. p. 97° (14 mm.)–108° (6 mm.); and 34.5 g. (18%) of the glutaconate (II), b. p. 110–114° (4 mm.), $n^{20}D$ 1.4502, d^{20}_{20} 1.0370, *MR* 51.91 (calcd. 51.22).[11] *Anal.* Calcd.

(9) Ost, *J. prakt. Chem.*, [2] **14**, 93 (1876).

(10) Reimer, *Ber.*, **11**, 793 (1878).

(11) Ruhemann, *J. Chem. Soc.*, **63**, 880 (1893).



for $C_{10}H_{16}O_4$: 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°; $n^{20}D$ 1.3817.

trans-α-**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°.[12] *Anal.* Calcd. for $C_6H_8O_4$: 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[13] which after recrystallization from ethyl acetate melted at 189–190° and decomposed with gas evolution when held slightly above the melting point.[13]

(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).

Ethyl α-**Methyl-**β-**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.), $n^{20}D$ 1.3857; 95 g. of a mixture consisting of ethyl methylmalonate and the acrylate (I), b. p. 51° (14 mm.)–63° (1 mm.), $n^{20}D$ 1.4157; 10 g. of an intermediate cut, b. p. 63–123° (1 mm.), $n^{20}D$ 1.4423; 17 g. (19%) of crude glutarate (III), b. p. 123–140° (1 mm.), $n^{20}D$ 1.4460; 4 g. of higher boiling material, b. p. 140–160° (1 mm.), $n^{20}D$ 1.4653; and 5 g. of residue. Refractionation of crude III gave the pure glutarate, b. p. 125° (1 mm.); $n^{20}D$ 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–

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°.[6]

Anal. Calcd. for $C_{13}H_{16}O_5$: 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°.[7]

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°.[9] Material prepared from other runs melted at 84–85.5°.

Anal. Calcd. for $C_{15}H_{13}O_7$: 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[9] 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[14] to melt at 310°. Ullmann and Brittner[15] 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 $C_9H_6O_7$: 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 β,β-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 β-ethoxyacrylic acid, m. p. 107–108° (no depression in melting point with an authentic sample).

Anal. Calcd. for $C_5H_8O_3$: 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.[11]

Summary

1. Ethyl methylmalonate and ethyl β-ethoxyacrylate (I) in the presence of benzyltrimethylammonium ethoxide gives ethyl α-methyl-β-glutaconate (II) and ethyl α-methyl-β-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.

PHILADELPHIA, PA. RECEIVED AUGUST 29, 1949

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

The Rearrangement of α,α'-Dibromoketones[1]

BY R. B. WAGNER AND JAMES A. MOORE

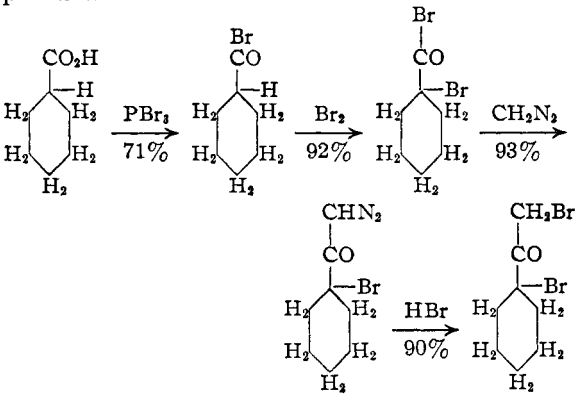
The conversion of an α,α'-dibromo-α-alkylketone to an unsaturated acid was first reported by Favorskii, who found that 1,3-dibromo-3-methyl-2-butanone, on treatment with alcoholic potassium hydroxide, gave β,β-dimethylacrylic acid in 60% yield.[2] This reaction has also been carried out with steroidal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

A closely related rearrangement of α,β-dibromoketones to unsaturated esters has been observed in the pregnane series,[4] and has recently been extended to aliphatic compounds.[5] In this later work, it has been shown that α,β-dibromo-α-alkylketones, on treatment with sodium methylate, yield β,γ-unsaturated esters.

$$RCHBrC(CH_3)BrCOCH_3 \xrightarrow[\text{Ether}]{NaOCH_3} RCH{=}C(CH_3)CH_2CO_2CH_3$$

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 α,α'-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 α,β-dibromoketone reactions. Since direct correlation of the two rearrangements was desired, three of these α,α'-dibromoketones have the same carbon skeleton as the compounds in the previously studied α,β-dibromoketone series. Thus, the two groups of compounds differ only in the position of one of the bromine atoms.

These α,α'-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.*: $RR'CHCOCH_3 \xrightarrow[2Br_2]{} RR'CBrCOCH_2Br$.

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 α,β-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 α,β-dibromoketone series, it is seen that the esters obtained from either type of ketone possess the same carbon skeleton. In every case, however, α,α'-dibromoketones give rise to α,β-unsaturated esters, and α,β-dibromoketones to esters with β,γ-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 α,β-dibromoketone. That the reaction actually involves a carbon skeleton rearrangement at least in the case of α,α'-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).