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Studies on Unsaturated 1,4-Dicarbonyl Compounds. VIII. Some New Derivatives of Dimethylfumaric Acid

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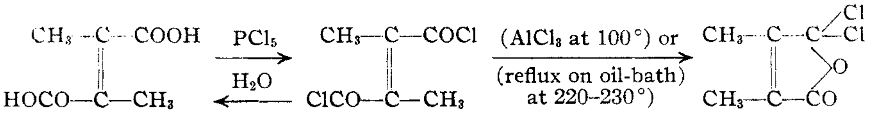
The substitution of two methyl groups in fumaric and maleic acids markedly alters the ease and in some cases the direction of rearrangement; for instance, maleic and citraconic acids with catalysts are rearranged into the *trans* isomers, but dimethylfumaric acid goes readily to dimethylmaleic anhydride under analogous conditions.[1] This paper deals with some related studies which were made preliminary to the synthesis of aryl dimethyl unsaturated 1,4-diketones and ketonic acids.[2]

Dimethylfumaryl Chloride (II).—Dimethylfumaric acid (I) forms a normal di-acid chloride (II) which is hydrolyzed rapidly and quantitatively back to the *trans* acid, reacts with methanol to give the diester (V) and with aniline to give the dianilide, and undergoes the Friedel and Crafts reaction to give diketones.[2] When it is heated with aluminum chloride at 100° it is rearranged completely into the *cis* acid chloride (III) which is known.[3] Heating without catalyst at boiling temperature also brings about this rearrangement, although considerable decomposition occurs as well.



I II III

The inversion of the *trans* acid chloride to the *cis* may be regarded as evidence that the latter has the dichlorocrotolactone structure (III), since this formulation would account for the rearrangement in terms of cyclization as the driving force. The energy change in inversion of the configuration alone, without other change in the molecule, would be expected to be very small but negative, and should lead if anything to rearrangement in the opposite direction (from *cis* to *trans*) as it does in the various inversions of maleic and citraconic acids and the unsaturated 1,4-diketones and ketonic esters. The easy rearrangement of dimethylfumaric acid to dimethylmaleic anhydride is obviously due to the formation of a stable ring as the driving force,[1a] and is therefore analogous.

The *cis* acid chloride[4] in contrast with the *trans* isomer reacts relatively

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(1) *Cf.* (a) Fittig, *Ber.*, **29**, 1842 (1896); (b) Fittig and Kettner, *Ann.*, **304**, 156 (1898); (c) Ott, *Ber.*, **61**, 2124 (1928).

(2) Lutz and Taylor, THIS JOURNAL, **55**, 1593 (1933).

(3) (a) Otto and Holst, *J. prakt. Chem.*, [2] **42**, 72 (1890). *Cf.* the rearrangement of dibromofumaryl chloride; (b) Ott, *Ann.*, **392**, 270 (1912).

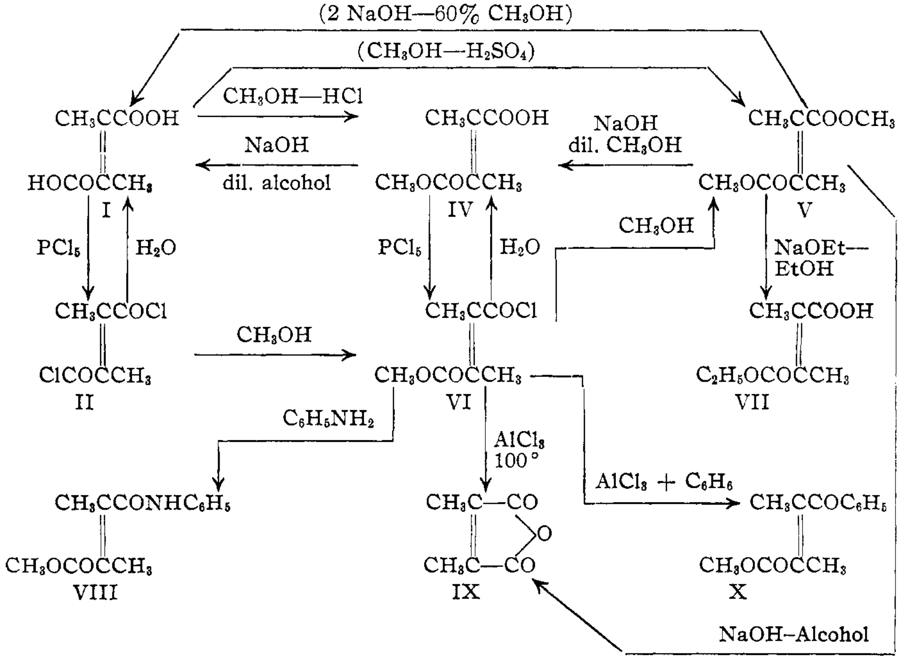
(4) *Cf.* also citraconyl chloride; Lutz and Taylor, THIS JOURNAL, **55**, 1168 (1933).

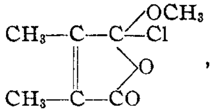
very slowly with water, a phenomenon which might possibly be accounted for on the basis of the cyclic formulation (III).

The Monoalkyl Acid Esters and Ester Chlorides.—The monomethyl acid ester (IV) is best obtained by the partial hydrolysis of the dimethyl ester (V) in dilute methanol with alkali, but when this reaction is carried out in ethanol–ether mixtures, displacement of methyl occurs and the mono-ethyl acid ester (VII) is obtained in good yield. The acid methyl ester may be prepared also, though in poorer yields, by partial esterification of the acid (I).

The monoalkyl ester acid chlorides (VI) are readily prepared from the acid esters by the action of phosphorus pentachloride, but are obtained in only very small yield by partial alcoholysis of the di-acid chloride. They are easily hydrolyzed back to the corresponding alkyl acid esters, are alcoholized to the diesters (V), react with aniline to give mono-anilides (VIII), and undergo the Friedel and Crafts reaction to give *trans*-aroyldimethylacrylic esters (X).[2]

The monomethyl ester mono-acid chloride (VI) is converted into dimethylmaleic anhydride with the loss of methyl chloride by heating with an excess of aluminum chloride at 100°. This reaction is analogous with the rearrangement of dimethylfumaryl chloride to the *cis* isomer, and with the dehydration of dimethylfumaric acid to the *cis* anhydride. The formation of the hypothetical *cis*-(ψ)-dimethylmaleic monomethyl ester mono-

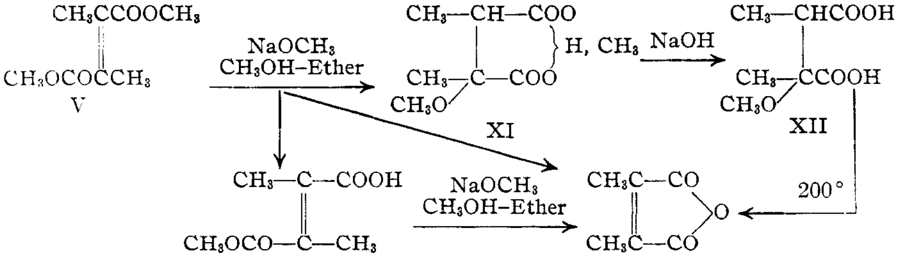


acid chloride,  , as an intermediate in the reaction, is possible.

Addition and Inversion.—Auwers[5] found that the hydrolysis of dimethylfumaric dimethyl ester with alcoholic alkali at room temperature gives regularly dimethylmaleic anhydride, but Curtius and Müller[6] using aqueous sodium hydroxide got normal hydrolysis without inversion of the configuration.

In the course of a number of experiments we have found also that both of the diesters and the monomethyl acid ester undergo rearrangement during hydrolysis in alcohol in which the water content is minimized; but invariably in dilute alcohol containing as much as 40% of water, nearly quantitative yields of dimethylfumaric acid are obtained with no detectable amounts of inversion or addition products. These rearrangements must occur during hydrolysis and not subsequently, since dimethylfumaric acid itself is stable under these conditions.

In the partial hydrolysis of dimethylfumaric dimethyl ester using one equivalent of sodium methylate in a methanol–ether mixture, the main product proved to be dimethylmethoxysuccinic monomethyl ester (XI), a compound formed obviously by the 1,4-addition of sodium methylate to the unsaturated system[7] with simultaneous hydrolysis of one of the two carbomethoxyl groups. The structure of the addition compound, except for the position of the methoxyl relative to the free carboxyl, was shown by hydrolysis to dimethylmethoxysuccinic acid (XII) and by subsequent pyrolysis to give dimethylmaleic anhydride. Small but significant amounts of dimethylmaleic anhydride and dimethylfumaric monomethyl acid ester (IV) were obtained as by-products of this reaction, but no dimethylfumaric acid.



In these hydrolytic reactions the reagent responsible for inversion, replacement of methyl by ethyl, and addition, must be sodium alcoholate

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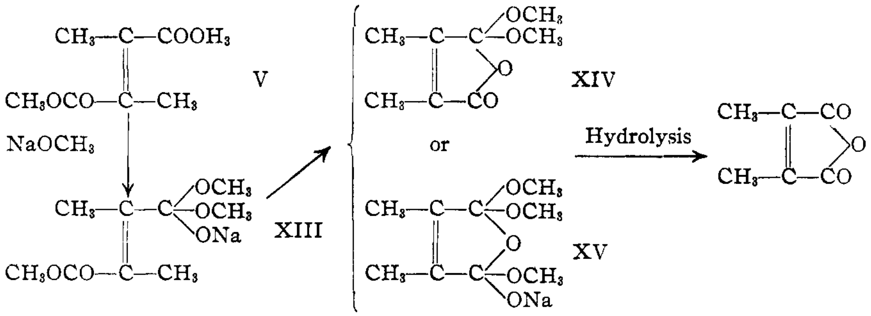
(5) Auwers, *Ber.*, **62**, 1678 (1929).

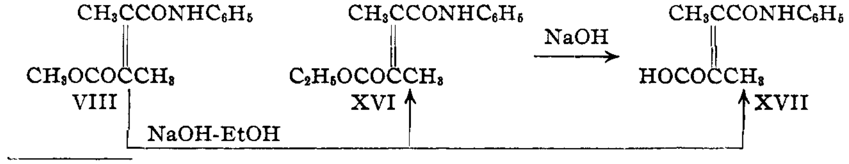
(6) Curtius and Müller, *ibid.*, **37**, 1272 (1904).

(7) Dimethyl fumarate undergoes this reaction readily in the presence of a trace of sodium methylate. (a) Perdue and Marshall, *J. Chem. Soc.*, **59**, 468 (1891). *Cf.* also (b) Claisen and Crismer, *Ann.*, **218**, 143 (1883); (c) Liebermann, *Ber.*, **26**, 1876 (1893); Hinrichsen, *Ann.*, **336**, 202 (1904); etc.

(rather than sodium hydroxide) because these reactions occur only in alcohol or alcohol–ether mixtures in which the effective alcoholate concentration is relatively high. Furthermore, a carbomethoxyl group is involved because dimethylfumaric acid in which this group is absent is stable under similar conditions. It seems unlikely that inversion of the configuration in the hydrolytic reactions involves actual addition of methanol to the ethylene linkage because such addition compounds are known and do not decompose easily. It is of course possible that of the two theoretically possible diastereoisomeric addition compounds, one might decompose much more easily than the other to lose the addenda and thus lead to inversion; or that an intermediate 1,4-addition product might be so unstable as to decompose similarly rather than undergo rearrangement into a stable dimethylsuccinic acid derivative. We are led to suggest another possible mechanism involving the addition of sodium methylate to a carbonyl group, followed by cyclization as the driving force in rearrangement, in which case possibly the *cis* di- or mono-alkyl esters are intermediates if the cyclic dihydroxylactone formulas suggested by Anschütz[8] are correct. In the illustration below inversion is shown as preceding hydrolysis, although partial hydrolysis might equally well take place first.



The Anilides.—Dimethylfumaryl chloride and the monomethyl and ethyl ester mono-acid chlorides react immediately in ether solution with aniline to give in each case the corresponding anilides. The two monoalkyl ester monoanilides both undergo partial hydrolysis in ethanolic alkali to the same monoanilide of dimethylfumaric acid (XVII). In the case of the monomethyl ester monoanilide (VII), curiously, although an excess of alkali was used, hydrolysis went only part way, but the methyl



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[8] Anschütz, *Ann.*, **254**, 168 (1889); **461**, 155 (1928). See also Ref. 6.

group was replaced by ethyl in the unhydrolyzed material. The dianilide was slowly hydrolyzed when boiled with alcoholic alkali, yielding, however, dimethylmaleic anhydride.

Experimental Part

Dimethylfumaric acid was prepared according to Ott.[1c] A few typical runs on the inversion of dimethylmaleic anhydride are summarized in the table.

No. of runs	Temp., °C.	Time of heating, hrs.	% Yields of A	B	C
5	180	45–48	50–60	23–39	9–12
3	180	64–72	32–44	38–43	11–14
4[a]	189–190	44–64	27–40	41–46	13–18

A, Dimethylmaleic anhydride; B, dimethylfumaric acid; C, methyl itaconic acid.

[a] Two of these runs started with methyl itaconic acid.

At 180°, sixty-five to seventy hours is required to establish equilibrium and a somewhat shorter time, forty-five hours, at 190°.

0.2 g. of the acid was allowed to stand for forty-one hours in 7 cc. of absolute methanol and 2.7 cc. of absolute ether containing 0.1 g. of dissolved sodium; 0.15 g. of the acid was recovered and identified, and no trace of dimethylmaleic anhydride was detected.

Dimethylfumaric dimethyl ester (V)[5] was prepared by adding 50 g. of dimethylfumaryl chloride dropwise with stirring to 25 cc. of absolute methanol over a period of one hour. A nearly quantitative yield of the ester crystallized on cooling (47.3 g.).

One gram of the dimethyl ester was allowed to stand overnight in 15 cc. of 60% methanolic sodium hydroxide (2 equiv.). The solution was then further diluted with water and extracted with ether. The aqueous solution of the sodium salts was then acidified, and the product isolated by extracting with ether; yield 0.78 g. (93%) of nearly pure dimethylfumaric acid.

Dimethylfumaryl Chloride (II).—Dimethylfumaric acid (168 g.) was allowed to react with 486 g. of phosphorus pentachloride. The mixture of acid chloride and phosphorus oxychloride was separated by two fractional distillations at 20 mm. using a 61-cm. Vigreux column; 193 g. of dimethylfumaryl chloride was obtained (91.5%) (together with an end fraction of 2.7 g. of dimethylmaleic anhydride; (b. p. 100–105° at 8 mm.)). The acid chloride is a nearly colorless oil; b. p. 79.5° at 22 mm.

Anal. Calcd. for $C_6H_6O_2Cl_2$: C, 39.79; H, 3.34. Found: C, 39.58; H, 3.24.

A sample of the acid chloride was hydrolyzed with water, on standing for twenty-four hours or shaking for one to two hours, to give the acid in quantitative yield.

Dimethylfumaric dianilide, $C_6H_5NHCOC(CH_3){=}C(CH_3)CONHC_6H_5$, was prepared by adding the di-acid chloride to an absolute ether solution of 4 equiv. of aniline; yield from 0.95 g. of acid chloride was 1.8 g.; cryst. as twinned rectangular prisms from ethanol; m. p. 267° (corr.).

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.47; H, 6.17. Found: C, 73.55; H, 6.17.

A small sample was boiled in dilute alcoholic sodium hydroxide for five hours. It was diluted with water and extracted with ether, from which, by extracting with hydrochloric acid, a solution of aniline was obtained which gave a characteristic precipitate with bromine. The aqueous solution of sodium salts was acidified and extracted with ether, from which dimethylmaleic anhydride was recovered by steam distillation.

Rearrangement of Dimethylfumaryl Chloride.—Two grams of the acid chloride was heated with 3.7 g. of anhydrous aluminum chloride at 100° for two and one-half hours. The mixture was hydrolyzed by allowing it to stand in water overnight. The products were extracted with ether. Steam distillation of the solid residue gave 0.65 g. of dimethylmaleic anhydride (47%). From the aqueous residue 0.1 g. of dimethylfumaric acid was recovered. The crude mixture containing the *cis* acid chloride was only partly hydrolyzed when shaken violently (machine) with water for four hours.

In a similar experiment a sample of dimethylfumaryl chloride was refluxed on an oil-bath (200–230°) for one and three-tenths hours. Some decomposition occurred, and a considerable yield of dimethylmaleic anhydride was isolated upon hydrolysis.

The Acid Esters of Dimethylfumaric Acid.—In the partial hydrolysis of the diester and the partial esterification of the acid, a convenient method of separating mixtures of the di-acid, monomethyl acid ester, and dimethyl ester, was followed; ether extraction of an alkaline solution removed the diester; acidification and a second ether extraction removed the acidic constituents which were isolated upon evaporation of the solvent; the acid ester was extracted from the insoluble dimethylfumaric acid by means of boiling ligroin from which it crystallized on cooling.

In the esterification of dimethylfumaric acid the two alpha methyl groups lower appreciably the rate of esterification, as was shown by comparing the low yields of acid ester and dimethyl ester from esterification in boiling 4% methanolic hydrogen chloride, with the better yields of the corresponding mesaconic acid derivatives obtained by Anschütz under similar conditions.[9]

Dimethylfumaric Monomethyl Acid Ester (IV).—The dimethyl ester (33.5 g.) was dissolved in 200 cc. of 95% methanol containing 11.2 g. of potassium hydroxide and allowed to stand for twenty hours. The mixture was diluted with water and the products separated as described above; yields, 5.5 g. (16.5%) of dimethyl ester, 17.5 g. (61%) of monomethyl ester, and 0.5 g. (2%) of dimethylfumaric acid; cryst. as needles from ligroin in which it is moderately soluble hot; m. p. 81° (corr.).

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.14; H, 6.38. Found: C, 53.13; H, 6.30.

A small sample of the monomethyl ester was treated with a slight excess of 2 equivalents of sodium dissolved in 2.5 parts of absolute alcohol and 0.8 part of dry ether, and allowed to stand for forty-one hours. An oily product (acidic) was obtained, from which a small yield of dimethylmaleic anhydride was isolated and identified. Hydrolysis in dilute alcohol gave dimethylfumaric acid in good yield.

Partial Esterification of Dimethylfumaric Acid.—A solution of 25 g. of dimethylfumaric acid in 100 g. of 4% absolute methanolic hydrogen chloride was refluxed for one hour, and was then decomposed in ice and sodium carbonate, and the products extracted and separated as described above; yields, 0.75 g. (2%) of the dimethyl ester, 3.4 g. (15%) of acid ester, and 11.6 g. (46%) of unchanged acid.

In another experiment 25 g. of the acid was allowed to stand for eighteen hours in saturated methanolic hydrogen chloride solution; yields, 6.5 g. (22%) of dimethyl ester, 8.89 g. (32%) of acid ester, and 4.5 g. (18%) of unchanged acid.

Partial alcoholysis of dimethylfumaryl chloride in benzene with one equivalent of methanol gave a mixture of products which consisted largely of diester and unchanged material and a small amount of mono-acid chloride monomethyl ester. The mixture was not easily separated and the mono-acid chloride was not isolated, but it was shown to be present by a Friedel and Crafts reaction on the mixtures, which gave small yields of *trans*-benzoyldimethylacrylic acid and dimethylfumaric monomethyl acid ester, both of which were derived from the mono-acid chloride.

Dimethylfumaric Monomethyl Ester Mono-acid Chloride (VI).—The acid ester (22.7 g.) and 31 g. of phosphorus pentachloride reacted to give a liquid mixture which was fractionally distilled at 20 mm.; yield of pure acid chloride, 20 g. (79%); colorless oil; b. p. 90–91° (corr.) at 20 mm.

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[9] Anschütz, *Ann.*, **353**, 139 (1907).

Anal. Calcd. for $C_7H_9O_3Cl$: C, 47.58; H, 5.14. Found: C, 47.14, 47.06; H, 5.89, 5.04.

One gram of the acid chloride was added to methanol; 0.72 g. of the dimethyl ester crystallized on cooling.

One gram reacted in less than two hours with water, from which on cooling 0.85 g. (95%) of monomethyl acid ester was isolated.

One-half gram of the acid chloride was heated at 100° with 2 g. of aluminum chloride for three hours. Gas evolution took place. The mixture was hydrolyzed and extracted with ether, which on evaporation and steam distillation gave 0.16 g. (32%) of dimethylmaleic anhydride.

Dimethylfumaric Monomethyl Ester Monoanilide (VIII).—Prepared by the action of the monomethyl ester monochloride on aniline in dry ether; cryst. slowly as microscopic scales from benzene and ligroin (requires careful seeding); m. p. 74–75° (corr.).

Anal. Calcd. for $C_{13}H_{15}O_3N$: C, 66.91; H, 6.44. Found: C, 66.79; H, 6.45.

Dimethylfumaric Acid Monoanilide (XVII).—The above monomethyl ester monoanilide (0.6 g.) was hydrolyzed with the calculated amount (1 equiv.) of sodium hydroxide in 5 cc. of 85% ethanol (forty-one hours standing) and gave an alkali-insoluble fraction (0.22 g. 36%) of m. p. 119–120°, identified as the corresponding monoethyl ester monoanilide. The hydrolyzed portion (alkali soluble), 0.36 g., (61%) crystallized from ether and ligroin; m. p. 195° (corr.).

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.76; H, 5.98. Found: C, 65.95; H, 6.04.

Dimethylfumaric Monoethyl Acid Ester (VII).—Dimethylfumaric dimethyl ester (47.3 g.) was treated with a solution of 6.6 g. of sodium in 350 cc. of 95% ethanol and 120 cc. of ether. The solution was allowed to stand for twenty-four hours and was then diluted with water and the ether layer separated, from which an oily di-ester (4.3 g.) was recovered and identified by hydrolysis to dimethylfumaric acid. The aqueous solution of the sodium salts was acidified and extracted with ether. After drying over sodium sulfate, the ether was evaporated and the oily residue distilled at 5 mm.; 2.3 g. (b. p. 84–86°) of dimethylmaleic anhydride, and 29.1 g. (b. p. 124–129°) (61.5%) of monoethyl ester of dimethylfumaric acid, were isolated and identified; 1.8 g. of dimethylfumaric acid was recovered from the residue in the distilling flask. The monoethyl ester is a colorless oil of b. p. 118° at 1 mm.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.78; H, 7.03. Found: C, 54.75, 54.85; H, 6.94, 6.89.

A sample was hydrolyzed on standing for thirty-six hours in a 10% solution of sodium carbonate, in which it dissolved easily with evolution of carbon dioxide. The mixture was distilled, and the ethyl alcohol liberated was converted into iodoform and identified by a mixed melting point. A test for methanol was negative.

One gram of the monoethyl ester was hydrolyzed by standing overnight in 10 cc. of a solution of one equivalent of sodium hydroxide in 50% ethanol; 0.83 g. of nearly pure dimethylfumaric acid was recovered and identified.

Dimethylfumaric Monoethyl Ester Mono-acid Chloride, $C_2H_5OCOC(CH_3)=C(CH_3)COCl$.—The monoethyl ester (21 g.) was allowed to react directly with one equivalent of phosphorus pentachloride. The resulting liquid products were fractionally distilled at 15 mm. using a 38-cm. Vigreux column; yield 20.7 g. (89%) of nearly pure acid chloride; colorless oil, b. p. 90–91° at 14 mm.

Anal. Calcd. for $C_8H_{11}O_3Cl$: C, 50.38; H, 5.82. Found: C, 49.93, 50.04; H, 5.72, 5.39.

Upon hydrolysis in 60% alcoholic potassium hydroxide, a nearly quantitative yield of dimethylfumaric acid was recovered and identified.

Dimethylfumaric Monoethyl Ester Monoanilide (XVI).—Prepared from the monoethyl ester monochloride with aniline in dry ether; yield 0.7 g. from 0.6 g. of acid chloride; cryst. as thin rectangular scales from benzene and ligroin, m. p. 121.5–122° (corr.).

Anal. Calcd. for $C_{14}H_{17}O_3N$: C, 68.00; H, 6.94. Found: C, 68.10; H, 6.90.

Hydrolysis of 0.1 g. with 1 equiv. of sodium in 2 cc. of 85% ethanol (forty-one hours standing) gave 0.08 g. of unchanged material and 0.015 g. of dimethylfumaric acid monoanilide which was identified.

1,2-Dimethylmethoxysuccinic Monomethyl Acid Ester (XI).—Dimethylfumaric dimethyl ester (37 g.) was allowed to stand for thirty-eight hours in a mixture of 250 cc. of absolute methanol and 100 cc. of commercial anhydrous ether, containing 5.3 g. of dissolved sodium. The solution was diluted with water and extracted with ether, from which 6.3 g. of a colorless oil was obtained on distillation at 2 mm. pressure (b. p. 70–80°). By oversight this oil was not investigated. It probably contained unchanged dimethylfumaric dimethyl ester and dimethylmethoxysuccinic dimethyl ester. The aqueous solution of sodium salts was acidified and extracted with ether and the products distilled at 2 mm.; the first fraction, b. p. 75–80°, solidified and was identified after recrystallization as dimethylmaleic anhydride. More was isolated from the second and third fractions, which consisted largely of dimethylfumaric monomethyl ester. The separation was made by extracting the mixture with dilute sodium carbonate solution and filtering quickly before the dimethylmaleic anhydride dissolved. The monomethyl ester was recovered from the filtrate. The fourth fraction proved to be nearly pure dimethylmethoxysuccinic monomethyl ester; colorless oil; b. p. 130–131° at 2 mm.

Anal. Calcd. for $C_8H_{14}O_5$: C, 50.50; H, 7.42. Found: C, 50.79; H, 7.26.

1,2-Dimethylmethoxysuccinic Acid (XII).—The monomethyl ester (1 g.) was dissolved in 10 cc. of 60% alcoholic sodium hydroxide (one equiv.) and allowed to stand for twenty hours. The mixture was diluted with water, washed with ether, and the aqueous layer acidified and extracted with ether, from which an oil was isolated on subsequent evaporation. The oil, taken up in benzene, deposited 0.2 g. of crystals; cryst. from benzene, m. p. 133.5° (corr.).

Anal. Calcd. for $C_7H_{12}O_5$: C, 47.70; H, 6.87. Found: C, 47.86; H, 6.88.

Pyrolysis.—The acid (0.04 g.) was heated to 200° in a small test-tube immersed in an oil-bath. On cooling, 4 drops of water was added and the mixture distilled. A small amount of dimethylmaleic anhydride solidified in the delivery tube and was identified by a mixed melting point.

Summary

A number of new derivatives of dimethylfumaric acid and its monomethyl and ethyl acid esters are described. Rearrangement of the *trans* configuration to the *cis*, addition, and replacement of methyl by ethyl, under the influence of alkali, are discussed.

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