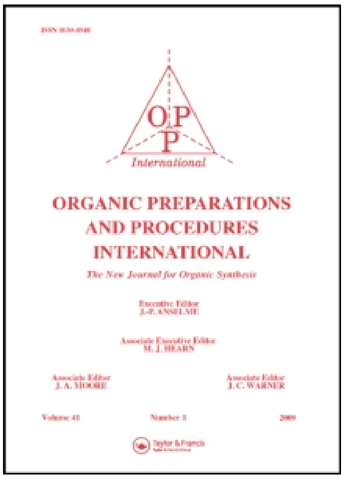

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PREPARATION OF n-MONOALKYL MALEATES AND n-MONO- AND DIALKYL FUMARATES

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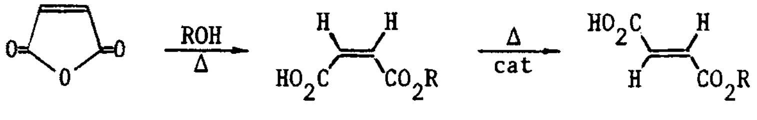
Recently we have established that methyl and ethyl esters of fumaric and maleic acids possess significant activity against Clostridium botulinum in canned meat, monomethyl fumarate being the most active.[1-3] It has also been demonstrated that dimethyl and diethyl fumarate have antifungal activity which is independent of pH of the medium.[4] These findings stimulated our interest to prepare higher n-alkyl fumarates and maleates over the range C_3H_7-$C_{18}H_{37}$ so that they can also be evaluated for antimicrobial activity.

The syntheses and characteristics of higher esters of fumaric and maleic acids have been only partially described.[5-10] A number of those esters are unknown and considerable amount of information is scattered in the literature which is not readily available.[11-15] Experimentations in our laboratory indicated that a number of the cited references are inefficient and time consuming. Recently we established a rapid and efficient method for the synthesis of monomethyl fumarate.[16] The current report establishes the general applicability of this method for the preparation of all desired monoalkyl maleates and fumarates according to the following scheme:



$R = CH_3$-$C_{18}H_{37}$

Increasing the chain length of the alcohols decreases the reactivity of the hydroxylic hydrogen. By reacting pulverized maleic anhydride with methyl, ethyl, n-propyl, and n-butyl alcohol at 30°, clear solution (i.e., the corresponding monoalkyl maleates) are obtained after 30, 120, 270, and 450 min, respectively. Further increases in chain length extended the reaction time by only a small degree. The reaction rate could be accelerated by increasing temperature; however, pure maleates were obtained only when the reaction was carried out below 60°. This was of particular importance when preparing maleates with R = C_3H_7-C_7H_{15}, which are oil-like liquids and cannot be purified by distillation. Monoalkyl maleates with R = CH_3 and C_2H_5 are distillable, while the higher monoalkyl maleates, R = C_8H_{17} and above, are solids and crystallize well from n-hexane, acetone, or ethanol.

Characteristic indexes of refraction and densities of distillable and undistillable maleates are summarized in Table 1. These data are compared with the values of Gordinskii et al.[11] It is apparent that their purification step is not practical and could be avoided by using our method for preparation of these maleates at a lower temperature. The yields and melting points of the solid maleates synthesized are listed in Table 2. Only a few compounds could be compared with the values given in the literature.[15,17] The remaining maleates may be regarded as unknown. No data of melting points could be found for several of the compounds even though these compounds are widely utilized for various purposes.[5,8,9,19,21] The melting points observed in the present study were lower for heptadecyl maleate.[18] With the one exception for R = $C_{18}H_{37}$,[15] all the references cited in Table 2 do not report the yields.

All compounds prepared in the present study were characterized by elemental analyses and IR spectra. A minimum purity of 98% for all the

TABLE 1. Liquid n-Monoalkyl Maleates

R	Yield (%)	n_D^{25}	d_{25}	Yield (%)	n_D^{20}	Literature d_{20}	Ref.
CH_3	98	1.4643	1.2503	55	1.4624	1.2457	11
C_2H_5	65	1.4593	1.1822	56.8	1.4569	1.1832	11, 5
C_3H_7	98.5	1.4555	1.1244	62	1.4580	1.1340	11
C_4H_9	98.7	1.4554	1.0916	62.6	1.4560	1.1030	11
C_5H_{11}	~98	1.4555	1.0629	83.4	1.4577	1.0787	11
C_6H_{13}	~98	1.4560	1.0455	67.8	1.4572	1.0525	11
C_7H_{15}	~98	1.4582	1.0254	71	1.4560	1.0315	11

TABLE 2. Solid n-Monoalkyl Maleates

R	Yield[a] (%)	mp. (°C)	Yield[b]	Literature mp. (°C)	Ref.
C_8H_{17}	87.9	32-32.5	-	22.5-23.5	15
C_9H_{19}	86.2	41-41.5	-	-	-
$C_{10}H_{21}$	85.0	45-45.5	-	42.2-46	15
$C_{11}H_{23}$	85.3	52-53	-	-	-
$C_{12}H_{25}$	86.5	58-58.5	-	53.2-54	15
$C_{13}H_{27}$	87.7	60.5-61	-	-	-
$C_{14}H_{29}$	86.2	65.5-66	-	-	-
$C_{15}H_{31}$	87.9	69-69.5	-	-	-
$C_{16}H_{33}$	89.3	71-71.5	-	69.5-70	15
			-	70-71.5	17
$C_{17}H_{35}$	84.9	75-75.5	-	100-100.5	18
$C_{18}H_{37}$	85.5	77.5-78	86	77.2-78	15
			-	80-81	9
			-	73-78	8

a) After recrystallization from n-hexane or ethanol. b) No values found in the literature, unless otherwise noted.

compounds was confirmed by HPLC. Examples of syntheses using procedure A and B are given in the Experimental section.

As expected, the higher n-alkyl fumarates and maleates displayed a very potent activity against C. botulinum, especially those with R = $C_{13}H_{27}$-$C_{17}H_{35}$, being about 1000 times as active as sodium nitrite. The unsymmetrical diesters, methyl n-alkyl fumarates, were less active and the symmetrical n-dialkyl fumarates were nearly inactive. The biological activity of these esters will be described separately.

n-Monoalkyl fumarates (Table 3) were prepared by isomerization of the corresponding maleates, using 0.5-1% fumaryl chloride or fumaric monoalkyl esters acid chloride as catalysts, using the procedure outlined for preparation of monomethyl fumarate,[16] with some adjustments of the temperature of isomerization. With increasing ester chain length, reaction times and temperatures of isomerization were gradually increased, but not over 120°. Two methods for the syntheses of monoethyl and n-propyl fumarates are given in the Experimental Section. Procedure B was used to prepare all the fumarates with R = C_4H_9-$C_{18}H_{37}$. The yields and the melting points for these fumarates are summarized in Table 3. Only a few examples of these compounds could be found in the literature, and no data on melting points could be found for fourteen of the compounds.

Klaban and Hudecek[22] prepared ten n-dialkyl fumarates with R = C_2H_5-$C_{10}H_{21}$ and $C_{16}H_{30}$ by azeotropic esterification of fumaric acid, using three moles alcohol, nine moles toluene, and 2% p-toluenesulfonic acid as a catalyst, and then refluxing the mixtures for 7.5-34 hrs. Shereshefsky and Wall[23] prepared dilauryl fumarate by heating at 110-130° for several hours equivalent amounts of fumaric acid with dodecyl alcohol. Neither reference indicated the yields (Table 4); however, our attempts indicated that the

TABLE 3. n-Monoalkyl Fumarates

R	Yield[a] (%)	mp. (°C) (bp/mm Hg)	Yield[b] (%)	Literature mp. (°C) (bp/mm Hg)	Ref.
CH_3	85.4	141-141.5	85.4	141-141.5	16
C_2H_5	84.5	68-69	70	66 (147/16)	27
C_3H_7	88.8	49-50 (114/0.3)	-	-	-
C_4H_9	85.6	45-46 (109/0.01)	-	78-80	20
C_5H_{11}	80.2	55-55.5	-	-	-
C_6H_{13}	83.5	52-52.5	-	-	-
C_7H_{15}	84.5	58.5-59	-	-	-
C_8H_{17}	82.7	65-65.5	-	-	-
C_9H_{19}	82.1	63-63.5	-	-	-
$C_{10}H_{21}$	83.3	75-75.5	-	-	-
$C_{11}H_{23}$	80.7	69.5-70	-	-	-
$C_{12}H_{25}$	82.0	80-80.5	-	-	-
$C_{13}H_{27}$	84.6	76-76.5	-	-	-
$C_{14}H_{29}$	83.9	81-82	-	-	-
$C_{15}H_{31}$	82.0	82-82.5	-	-	-
$C_{16}H_{33}$	83.3	84-85	-	-	-
$C_{17}H_{35}$	85.0	84-85	-	-	-
$C_{18}H_{37}$	85.8	88-88.5	85	79-80	20

a) After distillation or recrystallization. b) No values found in the literature, unless otherwise noted.

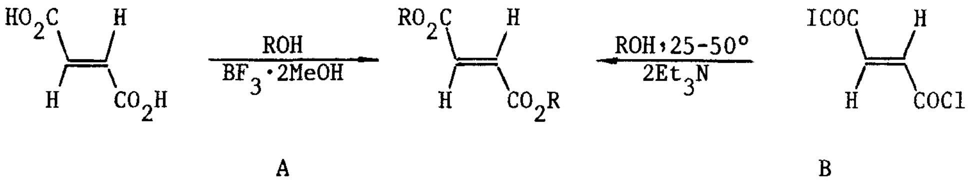
last procedure gives very low yields and is time consuming. As an alternative, two very fast and convenient methods were developed for preparation

TABLE 4. n-Dialkyl Fumarates

R	Yield[a] (%)	mp. (°C) (bp/mm Hg)	n_D^{23}	d_{23}	Literature		Ref.
					n_D^{20}	d_{20}	
CH_3	90.0	102-103.5	-	-	mp. 102°		28,23
C_2H_5	85.5	(45-7/0.05)	1.4380	1.0522	1.4404	1.0512	29
C_3H_7	86.5	(64-6/0.01)	1.4450	1.0122	1.4432	1.0113	29
C_4H_9	88.9	(90-2/0.15)	1.4472	0.9856	1.4464	0.9869	29
C_5H_{11}	94.9	(126/0.65)	1.4500	0.9775	1.4491	0.9663	29
C_6H_{13}	66.8	(150/0.80)	1.4515	0.9549	1.4518	0.9539	29
C_7H_{15}	83.0	(170/0.60)	1.4525	0.9410	1.4538	0.9432	29
C_8H_{17}	87.7	(190/0.80)	1.4543	0.9290	1.4553	0.9347	29
C_9H_{19}	80.5	25.5-26 (210-2/1.0)	1.4530	0.9372	mp. 25.4-26°		29
$C_{10}H_{21}$	80.2	31-31.5	-	-	-	-	-
$C_{11}H_{23}$	86.6	40-40.5	-	-	-	-	-
$C_{12}H_{25}$	80.0	46-46.5	-	-	mp. 45-46°		25
$C_{13}H_{27}$	80.1	(230/0.40)	1.4581	0.9050	-	-	-
$C_{14}H_{29}$	86.0	53.5-54	-	-	-	-	-
$C_{15}H_{31}$	78.5	58-59	-	-	-	-	-
$C_{16}H_{33}$	90.5	62-62.5	-	-	mp. 58.5-59.5		29
$C_{17}H_{35}$	75.1	67-67.5	-	-	-	-	-
$C_{18}H_{37}$	81.0	71.5-72	-	-	-	-	-

a) After distillation or recrystallization, yields refer to the procedure B, no yields were reported.

of n-dialkyl fumarates, with R = CH_3-$C_{18}H_{37}$ (Table 4), by direct esterification, using $BF_3 \cdot 2CH_3OH$ as a catalyst or by employing equivalent amounts of fumaryl chloride, alcohol, triethylamine, and n-hexane as a solvent.



Both methods were much faster compared with those reported in references 22 and 23, and were nearly quantitative. The second method was found to be more convenient for preparation of higher esters of R = $C_{14}H_{29}$ and larger. The first method is more economical and more suitable for industrial large scale preparations.

EXPERIMENTAL SECTION

The purity of these compounds was determined with a Water Associates[24] HPLC, model 440, with two pumps at 2000 psi, solvent programmer model 660, Hewlett-Packard integrator, model 3390, and μ-Bondapak C-18 column. Measured absorption at 280 nm in a solvent system 60% water, 32% methanol, and 8% acetic acid, flow rate 1 ml/min, sensitivity of the absorbance detector 0.1. IR spectra were determined (neat or as KBr pellets) on Perkin-Elmer 421 grating spectrophotometer. Maleic anhydride (99%) and most of the chemicals were obtained from commercial sources. Fumaryl chloride was prepared as described by Kyrides,[25] fumaric monomethyl ester monochloride was prepared using the procedure of Erlenmeyer and Schoenauer.[26]

Monomethyl Maleate.- A mixture of 19.60 g (0.2 mole) of maleic anhydride and 6.40 g (0.2 mole) of methanol was placed into a 100-ml reaction flask, tightly closed, and stirred (magnetic stirrer) for ~1 hr at room temperature until the solution became clear. This was then heated at 50° for about 30 min and distilled at 97-99°/0.01 mm Hg, bath at 120-122°. IR (film): 3060-2940, 1760-1720, 1630-1615 (sh), 1430, 1420-1390, 1260-1150, 990-980, 850-820, and 810-800 cm^{-1}; the purity was found to be 98.8% by HPLC.

A similar procedure was used to prepare all the other n-monoalkyl maleates (Tables 1 and 2), except that the initial reaction was conducted at 45-50°, then the clear solutions were heated for 1.5-2.5 hrs at ~60°. Maleates with R = C_3H_7-$C_{18}H_{37}$ exhibit additional IR band at 1165-1150 cm^{-1}.

Monoethyl Fumarate (Table 3).- Undistilled monoethyl maleate (0.2 mole) was mixed with 0.25 ml of fumaryl chloride and heated in a 100-ml round-bottomed flask for 2 hrs at 90-95°. The product was then stored at room temperature overnight, and the solidified material was recrystallized from *n*-hexane, ~15 ml/g. IR (KBr): 2980-2940, 1720-1710, 1690-1680, 1630, 1430-1415, 1355, 1310-1295, 1255, 1170-1160, and 990-975 cm^{-1}, purity 99.4% (HPLC).

The same procedure was used to prepare all the other *n*-monoalkyl fumarates (Table 3), except that 0.5 ml of the catalyst was used, and the isomerization temperature was gradually increased from 90 to 120°. All were recrystallized from *n*-hexane, ~5 ml/g. IR (KBr): 3080, 2960, 1715, 1680, 1630, 1460, 1425-1430, 1370, 1260, 1175-1165, 1110, 1030-1025, 985, 955, 920-910, and 770 cm^{-1}.

Dimethyl Fumarate (Table 4).

Procedure A.- A mixture of 23.20 g (0.2 mole) of fumaric acid, 150 ml of methanol, and 2 ml of $BF_3 \cdot 2CH_3OH$ was placed into a 250-ml reaction flask equipped with a condenser and magnetic stirrer, and heated with stirring for 2-3 hrs at 60-70° in a silicone bath. The temperature of the bath was then raised to 90° and about 70 ml of methanol was distilled, and the hot residue was filtered; the product crystallized from the filtrate almost immediately. This was stored for a few hours at 5°, filtered by suction, and dried at 56°/0.1 mm Hg. Upon concentration of the filtrate to about 50 ml, 1.8 g of additional product was obtained; total yield was 36.30 g. IR (KBr): 2980, 1715, 1440, 1310, 1195, 1160, 1110, 990, 773, 680, and 670 cm^{-1}, purity 98.2% (HPLC).

The same procedure was used to prepare diethyl fumarate. IR (film): 2980, 1720-1710, 1640, 1485, 1460-1435, 1290-1280, 1250, 1215, 1145, 1085, 1025, 970, and 850-835 cm^{-1}.

Procedure B.- Into a 200 ml two-neck flask equipped with a condenser, magnetic stirrer and a separatory funnel were placed 70 ml of methanol, then 15.29 g (0.1 mole) of freshly distilled fumaryl chloride was added dropwise over a period of 0.5 hrs; stirring was continued for an additional 0.5 hrs. The reaction mixture was then stored for a few hours at 5°. The crystalline material was filtered by suction and dried at 56°/0.1 mm Hg, yielding 13.05 g of dimethyl fumarate, purity 98.75% (HPLC).

The same procedure was used to prepare diethyl fumarate.

n-Dialkyl Fumarates (R = C_3H_7-C_8H_{14}).- These compounds were prepared by the two methods given above, except that one used exactly two moles of alcohols per one mole of acid. Also, when employing procedure A, time of the reaction was gradually increased from 4 to 6 hrs, and reaction temperature from 95 to 105°. Procedure B was used without any changes. IR (film): 2960, 2880, 1720-1710, 1640, 1455, 1385, 1340, 1280-1260, 1220, 1140, 1050, and 970 cm^{-1}.

Solid n-Dialkyl Fumarates (C_9H_{19}-$C_{18}H_{37}$).

Procedure A.- Exact equivalent amounts of alcohols were used as above. The temperature and time of the reaction were gradually increased to 115° and 8 hrs, respectively. The crude reaction product solidified at room temperature. The products were extracted with n-hexane and recrystallized from n-hexane using 4-6 ml/g, minimum purity 98%. Procedure B was modified slightly. Into the flask was placed 200 ml of n-hexane, 0.1 mole of alcohol, and 0.1 mole of triethylamine; fumaryl chloride (0.05 mole) was then added with stirring. The addition was completed in about 15 min, whereupon the reaction mixture was heated and stirred for 1 hr at 60-70°, filtered by suction, and the solvent removed by distillation. The solid residue was recrystallized from ethanol, using 4-7 ml/g. The IR spectrum was similar to those given above.

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