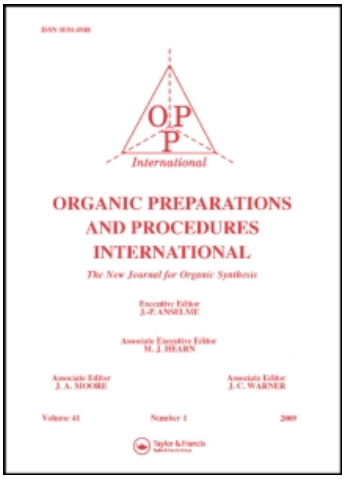


Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

PREPARATION OF METHYL a-ALKYL FUMARATES

Michael Dymicky[a]
[a] Eastern Regional Research Center, Agricultural Research Service, U. S. Department of Agriculture, Philadelphia, PA

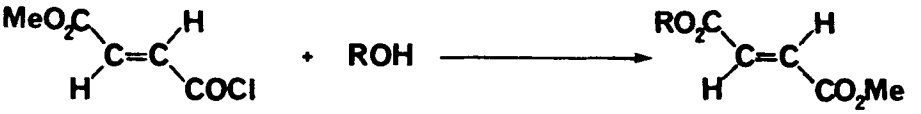
To cite this Article Dymicky, Michael(1986) 'PREPARATION OF METHYL a-ALKYL FUMARATES', Organic Preparations and Procedures International, 18: 3, 206 — 209
To link to this Article: DOI: 10.1080/00304948609458141
URL: http://dx.doi.org/10.1080/00304948609458141

PREPARATION OF METHYL n-ALKYL FUMARATES

Submitted by Michael Dymicky
(10/29/85)

Eastern Regional Research Center
Agricultural Research Service, U. S. Department of Agriculture
600 East Mermaid Lane, Philadelphia, PA 19118

n-Monoalkyl fumarates and maleates have been shown to possess a potent activity against Clostridium botulinum; somewhat lower, but still considerable, anticlostridial activity was displayed by the mixed unsymmetrical esters, methyl n-alkyl fumarates,[1,2] and their antibacterial activity is independent of the pH of the medium, which is often very useful and desirable. Since no reference could be found dealing with the preparation of these esters, we describe a method for their synthesis.



While ethyl-, n-propyl and n-butyl alcohols react easily with fumaric acid monomethyl ester monochloride without the use of solvent and triethylamine, higher alcohols react much more slowly and require the use of a base and solvent. The preparation of methyl n-nonyl fumarate is outlined below, and can be used as a model for all the esters with R $\geq$ C_5H_{11}. The identities of these esters were confirmed by elemental analyses, ir and mass spectra and their purity was ascertained by HPLC. The mass spectra of methyl n-alkyl fumarates exhibit three characteristic major ions, I-III, parent peaks with m/e 112.9, 130.75 and a peak which depends on the nature of R. The relative abundance of I and II is about 85 and 100% respectively.[3] The abundance of the parent peak III ranges from 20 to 2.5%. As R increases the abundance of III decreases.

EXPERIMENTAL SECTION

Fumaric acid monomethyl ester monochloride was prepared as described by Erlenmeyer and Schoenauer.[4] Alcohols and other chemicals were obtained from commercial sources. IR spectra were determined (films or KBr pellets) on Perkin-Elmer[5] 421 grating spectrophotometer. The purity of these esters was determined with a Water Associates 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. Mass spectra were determined using low resolution quadrupole Hewlett-Packard GC/mass spectrometer, model 5992B, fitted with a Scientific Glass Engineering open split adaptor, and a 0.25 mm x 50 m silica column coated with methyl silicone (0.5 μm), manufactured by Quadrex Corporation. The He flow rate was 3.0 ml/min at the elution temperature of the compound, with a purge flow rate of 0.5 ml/min, and the injector port temperature was 150°. The oven temperature was programmed from 30 to 250°, at a rate of 10°/min. The elution peaks were scanned from 29 to 350 m/e, at a rate of 80 scans/min.

Methyl Ethyl Fumarate.- To 14.85 g (0.10 mole) of fumaric acid monomethyl ester monochloride in a 100 ml reaction flask, equipped with a condenser, magnetic stirrer, separatory funnel and a silicone bath was added dropwise 25 ml of ethanol over a period of 15 min. The temperature of the bath was raised to 60° and the mixture was stirred and heated at that temperature for an additional 30 min. The ethanol was then removed under reduced pressure at 25° and the ester distilled at 40-41°/0.01 mm Hg, whereupon 13.30 g (84% yield) was obtained, n_D^{25} 1.4408, d_{25} 1.0717. IR (film): 2960, 2922, 1850, 1725, 1640, 1435, 1375, 1300-1140, 1025 and 960 cm^{-1}.

The same procedure was used to prepare methyl n-propyl- and methyl n-butyl fumarates.

Methyl n-Nonyl Fumarate.- To a stirred mixture of 7.43 g (0.05 mole) of fumaric acid monomethyl ester monochloride, 7.22 g (0.05 mole) of n-nonanol and 300 ml n-hexane in a 500 ml reaction flask, equipped as described

TABLE 1. Methyl n-Alkyl Fumarates[a]

R	Bp°C/mm Hg	n_D^{25}	d_{25}	Yield (%)	Elemental Analyses Calcd(Found) C	H
C_2H_5	40-1/0.01	1.4466	1.0717	84	53.18(53.42)	6.32(6.15)
C_3H_7	50-2/0.01	1.4444	1.0494	82	55.83(55.56)	6.97(6.80)
C_4H_9	61-2/0.01	1.4460	1.0396	83	58.08(57.75)	7.52(7.68)
C_5H_{11}	74-6/0.1	1.4470	1.0240	77	60.01(59.65)	7.99(8.12)
C_6H_{13}	85-7/0.1	1.4483	1.0181	82	61.70(61.89)	8.40(8.25)
C_7H_{15}	97-8/0.1	1.4490	0.9938	77	63.13(62.82)	8.83(8.67)
C_8H_{17}	104-5/0.1	1.4502	0.9745	87	64.43(64.18)	9.08(9.22)
C_9H_{19}	107-9/0.1	1.4528	0.9779	78	65.59(65.16)	9.43(9.29)
$C_{10}H_{21}$	114-6/0.1	1.4540	0.9775	81	66.63(66.28)	9.69(9.50)
$C_{11}H_{23}$	(33-33.5)	--	--	79	67.57(67.30)	9.92(10.08)
$C_{12}H_{25}$	(35-36)	--	--	76	68.41(68.30)	10.13(9.85)
$C_{13}H_{27}$	(36-37)	--	--	67	69.19(68.78)	10.32(10.09)
$C_{14}H_{29}$	(36-36.5)	--	--	72	69.89(69.36)	10.49(10.57)
$C_{15}H_{31}$	(38-39)	--	--	78	70.54(70.13)	10.65(10.42)
$C_{16}H_{33}$	(44-44.5)	--	--	74	71.14(70.78)	10.80(11.08)
$C_{17}H_{35}$	(47-48)	--	--	72	71.70(71.35)	10.85(10.72)
$C_{18}H_{37}$	(52-53)	--	--	70	72.20(72.43)	11.06(10.88)

a. These esters are mentioned with no data in references 6, 7 and 8.

above, was added dropwise (30 min) 5.05 g (0.05 mole) of triethylamine dissolved in 50 ml n-hexane. The temperature of the bath was then raised to 60-70° and maintained at that temperature for two additional hrs. The triethylamine hydrochloride which had formed was collected and n-hexane was removed from the filtrate under reduced pressure. The residue was distilled at 107-109°/0.1 mm Hg, whereupon 10.84 g (78% yield) of methyl n-nonyl fumarate was obtained, n_D^{25} 1.4528, d_{25} 0.9779.

REFERENCES

1. M. Dymicky, J. L. Smith and M. Bencivengo. Patent Application Serial No. 611,042; Federal Register 50 (97), May 20, 1985; M. Dymicky, M. Bencivengo, R. L. Buchanan and J. L. Smith, (in press); C. N. Huhtanen, M. Dymicky and H. Trenchard, 41st Ann. IFT Meeting, Atlanta, GA, June 7-10, 1981, Paper No. 21. "Methyl and Ethyl Esters of Fumaric Acid as Substitutes for Sodium Nitrite for Inhibiting Clostridium botulinum Spore Outgrowth in Bacon", p. 98.

2. M. Dymicky, Org. Prep. Proced. Inter., 15, 233 (1983); M. Dymicky and R. L. Buchanan, ibid., 17, 121 (1985).

3. R. M. Silverstein and G. C. Bassler, "Spectroscopic Identification of Organic Compounds", 2nd Ed., p. 23, John Wiley & Sons, Inc., New York, 1967.

4. H. Erlenmeyer and W. Schoenauer, Helv. Chim. Acta, 20, 1008 (1937).

5. Reference to brand or firm name does not constitute endorsement by U.S. Department of Agriculture over others of a similar nature not mentioned.

6. J. E. Fields and J. H. Johnson (to Monsanto Co.) U. S. 3,201,351; C. A. 63, P11231f (1965).

7. G. R. Barrett (to Monsanto Co.), U. S. 2,537,016; C. A. 45, 3169i (1951).

8. Essor Res. & Engineering Col., Neth. Appl. 6,508,475; C. A. 64, 17864f (1966).

A SELECTIVE SYNTHESIS OF 5-*p*-AMINOPHENYLBARBITURIC ACID

Submitted by (10/29/85) Frank V. Bright[†], Richard A. Bunce[*] and Linda B. McGown

Department of Chemistry
Oklahoma State University
Stillwater, OK 74078

We recently needed samples of fluorescently labelled phenobarbital for the development of a fluoroimmunoassay for this barbiturate.[1] Since this technique relies upon competitive binding of labelled and unlabelled drug to an antibody, the fluorescent tag must