Registry No.—Ia oxalate, 17968-59-1; Ia $HClO_4$, 18026-68-1; Ib, 17968-58-0; Ic oxalate, 18006-26-3; Ic HCl, 18006-27-4; Ic MeI, 18006-28-5.

A Small-Scale Synthesis of Mevalonolactone and Its 3-Ethyl-2-^{14}C Homolog

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Mevalonic acid (or its lactone, 3,5-dihydroxy-3-methylpentanoic acid γ-lactone, **2b**) has long been recognized as a precursor of the isoprene unit used by living systems in biosynthesis.[1] Analogs of mevalonolactone, however, have not been extensively tested in biological systems. Tamura, *et al.*,[2] and Stewart and Woolley[3] have synthesized several homologs and tested them for antimetabolic activity, but the question whether 3,5-dihydroxy-3-ethylpentanoic acid γ-lactone (**2a**, the 3-ethyl homolog of mevalonolactone) is metabolized by living systems was left unanswered. In order to obtain material for such a study,[4] we undertook the synthesis of **2a** labeled with ^{14}C in the 2 position.

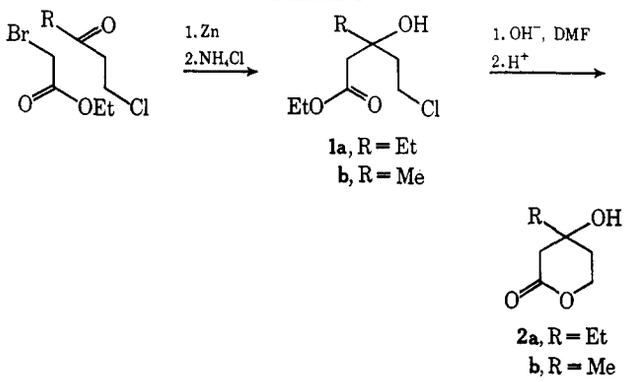
Compound **2a** has been synthesized by Tamura and Takai[5] by the method used for mevalonolactone.[6] The tetrahydropyranyl ether of the appropriate 3-keto alcohol was treated with allylmagnesium bromide; the protecting group was removed; the terminal olefin was cleaved by ozonolysis; and the lactone was obtained upon work-up, during which cyclization of the dihydroxy acid occurred.

Several other mevalonolactone syntheses have been reported. Those based on Hoffman's synthesis[7] involve a Reformatski reaction between ethyl bromoacetate and 4-acetoxy-2-butanone.[8-10] After saponification of the resulting diester, the lactone forms upon acidification. Hulcher and Hosick[11] reported an internal Reformatski reaction of 4-(bromoacetoxy)-2-butanone prepared from bromoacetyl bromide and 4-hydroxy-2-butanone. Cornforth and coworkers have reported syntheses of mevalonolactone labeled in both the 4 position and methyl group, and the 4 position alone.[12] They have also synthesized stereospecifically the (+) and (−) forms from (−)- and (+)-linalool, respectively.[13]

For the small-scale preparation of radioactively labeled **2a** or **2b**, each of the above sequences suffers from one or more of the following deficiencies: (a) three or more steps in the reaction scheme, (b) relatively low over-all conversion, (c) commerical unavailability of one of the starting materials. In addition, the final product is distilled in each of these procedures, thus making it desirable to devise another method of purification for small-scale work. We have therefore developed the procedure described below.

Compounds **2a** and **2b** have been prepared by the sequence shown in Scheme I. Where R = Et, the

SCHEME I



yield of purified product in each step is generally about 65–70%.[14] This procedure has the advantages that the sequence consists of only two steps, the starting materials are commercially available, the use of tlc in purification permits very small-scale reactions, and the product can be labeled at the 1 or 2 positions *via* the ethyl bromoacetate and at the 3 position or alkyl group *via* the acid chloride used in preparation of the chloro ketone.[15,16]

Experimental Section

Infrared spectra were determined with a Beckman Model IR-8 or a Perkin–Elmer Model 237-B spectrophotometer. The nmr spectra were determined with a Varian Model A-60 spectrometer. The chemical shifts are expressed in τ values relative to tetramethylsilane as an internal standard. Gross appearance of the peaks is reported, though some signals show higher order splitting. Mass spectra were obtained with an LKB-9000 combined gas chromatograph–mass spectrometer.[17] All spectra reported, with the exception of the ir spectrum of **2a**, are of nonradioactive materials. Preparative tlc was conducted using air-dried, unactivated[18] Mallinckrodt TLC-7GF[19] silicic acid. The 1-chloro-3-pentanone and 4-chloro-2-butanone were purchased from Aldrich and Chemical Procurement Labora-

(1) R. B. Clayton, *Quart. Rev.* (London), **19**, 168, 201 (1965).
(2) S. Tamura, G. Tamura, M. Takai, S. Nakamura, and T. Shiro, *Bull. Agr. Chem. Soc. Jap.*, **22**, 202 (1958).
(3) J. M. Stewart and D. W. Woolley, *J. Amer. Chem. Soc.*, **81**, 4951 (1959).
(4) This study is being carried out by Dr. C. C. Sweeley and his students.
(5) S. Tamura and M. Takai, *Bull. Agr. Chem. Soc. Jap.*, **21**, 394 (1957).
(6) S. Tamura and M. Takai, *ibid.*, **21**, 260 (1957).
(7) C. H. Hoffman, A. F. Wagner, A. N. Wilson, C. H. Shunk, D. E. Wolf, F. W. Holly, and K. Folkers, *J. Amer. Chem. Soc.*, **79**, 2316 (1957).
(8) O. Isler, R. Rüegg, J. Würsch, K. F. Gey, and A. Pletscher, *Helv. Chim. Acta*, **40**, 2369 (1957).
(9) J. Cornforth, R. Cornforth, C. Popjak, and I. Youhotsky-Gore, *Biochem. J.*, **69**, 146 (1958).
(10) A. L. Remizov and G. A. Tsvetkova, *Sintez Prirodn. Soedin., ikh Analogov i Fragmentov, Akad. Nauk SSSR, Otd. Obschi. i Tekhn. Khim.*, 129 (1965); *Chem. Abstr.*, **65**, 614a (1966).
(11) F. H. Hulcher and T. A. Hosick, U. S. Patent 3,119,842 (1964); *Chem. Abstr.*, **60**, 10554g (1964).
(12) J. W. Cornforth, R. H. Cornforth, A. Pelter, M. G. Horning, and G. Popjak, *Tetrahedron*, **5**, 311 (1959).
(13) R. H. Cornforth, J. W. Cornforth, and G. Popjak, *ibid.*, **18**, 1351 (1962).
(14) In the single preparation of mevalonolactone (R = Me), the hydrolysis step went in lower yield (52%).
(15) F. Sondheimer and R. B. Woodward, *J. Amer. Chem. Soc.*, **75**, 5438 (1953).
(16) F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1376 (1959).
(17) We wish to thank the National Institutes of Health for the grant with which this instrument was purchased, and Dr. C. C. Sweeley and Mr. John Naworal for the spectra.
(18) The use of freshly prepared and activated layers can cause extensive dehydration during attempted purification of the lactone.
(19) In this system, cleaner products are obtained from Mallinckrodt TLC-7GF silicic acid than from Merck silica gel G.

tories, respectively,[20] and were evaporatively distilled and stored in a freezer over type 5A molecular sieve prior to use. Gas chromatographically analyzed ethyl bromoacetate-2-^{14}C (1.5 mc; 2.09 mc/mmol) was purchased from Mallinckrodt Nuclear. Syringes were dried, when necessary, by flushing with ether which had been dried over type 4A molecular sieve. The molecular sieve was heated for at least 6 hr at 180° in a vented oven before use.

Ethyl 3-Ethyl-3-hydroxy-5-chloropentanoate-2-^{14}C (1a).—A micro stirring bar and 69.5 mg (1.06 mmol) of freshly treated zinc[21] were introduced into a 3-ml flask blown from 8-mm tubing. The flask was stoppered with a silicone rubber gas chromatographic septum and dried by flushing *via* hypodermic needles with dry nitrogen while it was heated at about 70° with a hot air blower for about 6 hr. The ethyl bromoacetate-2-^{14}C (0.718 mmol, calculated from the specific activity assuming quantitative transfer—not actually realized) was diluted with 300 μl of dry ether and transferred by syringe onto approximately 0.5 g of type 4A molecular sieve in a serum-cap-stoppered 5-ml dry pointed flask. Ether rinsings (four 300-μl portions) from its vial were similarly injected. About 82 μl (87.6 mg, 0.727 mmol) of 1-chloro-3-pentanone was injected into a flame-dried septum-stoppered pointed test tube, weighed, diluted with 100 μl of dry ether, and transferred by syringe onto the molecular sieve. One 100-μl rinsing from the test tube was also injected. The reagent mixture was allowed to dry for 3 hr[22] and was then injected into the reaction flask. The molecular sieve was rinsed with dry ether (two 250-μl portions), and the rinsings were injected into the reaction flask. The septum was sealed with a few drops of melted paraffin wax, and the reaction mixture stirred at room temperature for 18 hr. At the end of this time the solution was clear and the zinc was noticeably depleted. A further 48 hr of stirring produced no visible change. The reaction mixture was quantitatively transferred to a 5-ml flask, and hydrolyzed by magnetically stirring it for 0.5 hr with 300 μl of saturated ammonium chloride solution and 200 μl of water. The mixture was extracted 20 times by stirring with small portions of ether, the ether being withdrawn by syringe. The ether solution was dried ($MgSO_4$) and concentrated, leaving 115.4 mg of light yellow liquid. This was purified by tlc using chloroform–carbon tetrachloride (36:14) for development. The plate was scraped from just above the product front, visible as a light yellow line, to the top of the origin. The silicic acid was washed in a fine sintered funnel with several small portions of ether and the ether stripped, leaving 101.3 mg (68%) of purified product.

Analysis of the tlc-purified product by the combination vpc–mass spectrograph shows the presence of a small amount of the dehydrochlorinated compound, whose mass spectrum (70 eV) shows *m/e* 172 (molecular ion, small) and abundant fragment peaks at *m/e* 154, 143, 126, 109, 97, 81, 55, and others.

Spectra of the chlorohydroxy ester: ir (between salt plates) 3497 (OH), 1720 (C=O), 1193 (O—C), 715 (C—Cl) cm^{-1}; nmr (CCl_4) τ 5.82 (2 H, quartet, J = 7 cps, OCH_2CH_3), 6.28 (1 H, s, OH), 6.48 (2 H, t, CH_2CH_2Cl), 7.57 (2 H, s, $R_3CCH_2CO_2$), 7.9–9.3 ppm (10 H, multiplet); mass spectrum (70 eV) no molecular ion peak, chlorine-containing ion peaks in approximate 1:3 ratios at *m/e* 211, 209, 193, 191 (these high mass ions are visible only when the spectrum is off scale), 181, 179, 165, 163, 135, 133, 123, 121, abundant fragment peaks at *m/e* 145, 99, 91, 63, 57, and others.

3,5-Dihydroxy-3-ethylpentanoic Acid ζ-Lactone-2-^{14}C (2a).—A solution of 101.3 mg (0.485 mmol) **1a** in 180 μl of N,N-dimethylformamide and 40 μl water was stirred magnetically and heated at *ca.* 50° in a water bath, and 182 μl of *ca.* 5.4 *N* KOH solution (0.97 mmol) was added dropwise from a syringe. The first 90 μl was added at a rate of 1 drop/30 sec, the remainder at 1 drop/5 min. After addition of the base, the solution was stirred at 50° for 2 hr, during which a small amount of white solid formed. The mixture was cooled, and acidified to *ca.* pH 3 with 18% HCl, then acidified to *ca.* pH 2 with 5% HCl (short-range indicator paper was used). The acid solution was stirred for 10 min, transferred by means of three DMF and three ether washes into 10 ml of Spectro-Grade $CHCl_3$ which contained a large amount of magnesium sulfate, and stirred vigorously for a few minutes. The $MgSO_4$ was filtered on a fine sintered-glass funnel and washed with chloroform. On a rotary evaporator the filtrate was stripped of chloroform at 27° (*ca.* 20 mm) and then of DMF during 0.5 hr at 59–60° (0.2–0.8 mm); an ir spectrum (between salt plates) of the 66.6 mg of light yellow material remaining showed no band for DMF at 1664 cm^{-1}. After recovery of the material from the salt plates, the crude lactone was purified by tlc using ether for development. The plate was scraped from the product front, which was easily visible under a uv light or as a dampness of the layer, to the top of the origin. The silicic acid was washed with Spectro-Grade $CHCl_3$ (14 5-ml portions), and the solution was concentrated. The product consisted of 49.6 mg (71%) of light yellow liquid.

Spectra of the homomevalonolactone: ir (between salt plates) 3440 (OH), 1741–1717 (C=O), 1269 and 1236 (O—C), and nothing from the carbonyl to 1500 cm^{-1}; nmr ($CDCl_3$) 5.3–6.1 (2 H, multiplet, OCH_2CH_2), 7.18 (1 H, s, OH), 7.57 (2 H, s, $R_3CCH_2CO_2$), 8.1–8.7 (4 H, multiplet, $CH_3CH_2C(OH)(R)CH_2CH_2O$), 9.08 (3 H, t, CH_3CH_2) ± 3 ppm; mass spectrum (70 eV) molecular ion at *m/e* 144, abundant fragment peaks at 126, 115, 85, 71, 57, 53, and 43.

Radioanalysis of the Homomevalonolactone.[23]—In a liquid scintillation counter 1 μl of a 1:10 diluted solution of homomevalonolactone in $CHCl_3$ gave 3.43 × 10^5 dpm. An autoradiogram of 2 μl of this solution chromatographed on a 10% $AgNO_3$–Kieselgel G plate using chloroform–acetone (9:1) for elution showed a single spot. This system separates the hydroxy lactone from unsaturated lactone and open acid. A radiochromatogram of 1 μl of the above solution on a Packard Tri-Carb liquid scintillation spectrometer equipped with a 6-ft glass column packed with 3% OV-1 on Gas Chrom Q showed no detectable impurity except for a small amount of radioactivity which came off the column with the solvent and is attributed to decomposition in the instrument. Since the product peak on the vpc trace was a factor of 33 off scale, and we should be able to see a peak 1% of full scale, the maximum amount of impurity is estimated by vpc to be less than 0.03%.

Comments on Gas Chromatography of the Homomevalonolactone.—The presence of impurity peaks between the solvent and product peaks seems to be a function of instrumental conditions. An injection of a chloroform solution of reasonably pure homomevalonolactone onto a 10 ft × 1/8 in. steel column packed with 3% OV-1 on Gas Chrom Q (glass-lined injection port at 200°, column at 110°) showed a small impurity peak of 5% of full scale, while the product peak was off scale. Successive identical injections introduced two new impurity peaks which grew relatively larger with each injection. Upon conditioning the column for 10 min at 280°, reestablishing the operating conditions, and reinjecting the same solution, the cycle was repeated. Injection onto a freshly conditioned column followed by programming to 285° showed no spurious impurity peaks and only normal baseline rise. Another similar OV-1 column did not exhibit this behavior, but instead gave the above impurity peaks persistently; they were only slightly reduced upon reconditioning. The fully silanized glass column in the LKB-9000 combined vpc–mass spectrometer did not exhibit this anomalous behavior.

Ethyl 3-Methyl-3-hydroxy-5-chloropentanoate (1b).—Compound **1b** was prepared in 66% yield by the method given above for compound **1a** from 0.645 mmol of ethyl bromoacetate and 0.70 mmol of 4-chloro-2-butanone. Analysis of the tlc-purified product by the vpc–mass spectrograph showed relatively more dehydrochlorinated impurity than was present in its homolog **1a**. The impurity's mass spectrum (70 eV) shows *m/e* 158 (molecular ion, small) and abundant fragment peaks at *m/e* 143, 140, 131, 112, 97, 95, 88, 71, 55, and others. The mass spectrum of the chlorohydroxy ester **1b** shows no molecular ion peak, but abundant fragment peaks in approximate 1:3 ratios at *m/e* 181, 179 and 109, 107, and other fragments at *m/e* 143, 131, 113, 107, 91, 85, 71, and others.

3,5-Dihydroxy-3-methylpentanoic Acid δ-Lactone (2b).—Mevalonolactone (**2b**) was prepared by the method given above for compound **2a** from 80.7 mg of chlorohydroxy ester **1b** which contained a significant amount of dehydrochlorinated impurity. Assuming pure **1b** for purposes of calculation, the yield of the tlc-purified mevalonolactone was 52%. The ir and nmr spectra

(20) "Chem Sources," 8th ed, Directories Publishing Co., 1967, lists Frinton Laboratories, S. Vineland, N. J. 08360, as anad ditional source of 4-chloro-2-butanone.

(21) Zinc granules were washed successively with dilute HCl, water, acetone, absolute ethanol, and absolute ether. Traces of solvent were removed in a vacuum desiccator.

(22) If the ether (1800 μl) is saturated with water rather than predried, the solution is sufficiently dry at the end of 10 hr.

(23) We wish to thank Miss Sandy Baumann of Dr. C. C. Sweeley's research group for these results.

match Sadtler No. 21402[24] and Varian Associates No. 466[25] standard spectra, respectively.

Registry No.—**1a** (2-^{14}C), 17923-95-4; **1b**, 17943-79-2; **2a** (2-^{14}C), 17923-96-5; **2b**, 503-48-0.

(24) Sadtler Standard Spectra, Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1967.
(25) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Vol. 2, Varian Associates, 1963.

Participation of a Cyclopropane Ring in Extension of Conjugation

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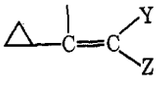
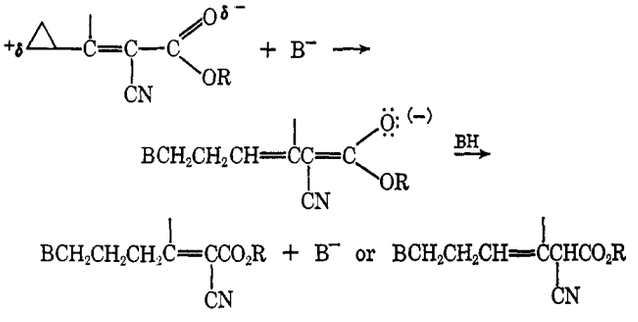
An earlier report from this laboratory[1] described ring-opening addition reactions between nucleophilic reagents and cyclopropanes which were substituted on one carbon atom of the ring by two electron-withdrawing groups.

In one simple extension of this work, the study reported here was made of the reactions of nucleophiles with structures of the type



where Y and Z represent electron-withdrawing groups such as ester and nitrile. In such reactions, extension of conjugation by participation of the cyclopropane ring would result in ring-opening 1,6 addition, whereas

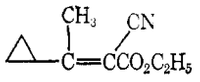


lack of participation by the ring would result in simple addition to the carbon–carbon double bond.

There are conflicting reports with respect to the ability of a cyclopropane ring to participate in conjugation (see typical ref 2–7, and references cited therein).

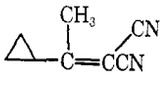
(1) J. M. Stewart and H. H. Westberg, *J. Org. Chem.*, **30**, 1951 (1965).
(2) R. C. Fuson and F. N. Baumgartner, *J. Amer. Chem. Soc.*, **70**, 3255 (1948).
(3) L. I. Smith and E. R. Rogier, *ibid.*, **73**, 3840 (1951).
(4) R. H. Eastman, *ibid.*, **76**, 4115 (1954).
(5) A. Pawda, L. Hamilton, and L. Norling *J. Org. Chem.*, **31**, 1244 (1966).
(6) W. G. Dauben and E. J. Deving, *ibid.*, **31**, 3794 (1966).
(7) T. A. Wittstruck and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **89**, 3810 (1967).

Using the method described by Cope, *et al.*,[8] for acid-catalyzed condensation of ketones with active methylene compounds, the desired starting materials, ethyl 2-cyano-3-cyclopropyl-2-butenoate (compound **1**),



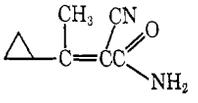
1

2-cyano-3-cyclopropyl-2-butenenitrile (compound **2**),



2

and 2-cyano-3-cyclopropyl-2-butenamide (compound **3**)

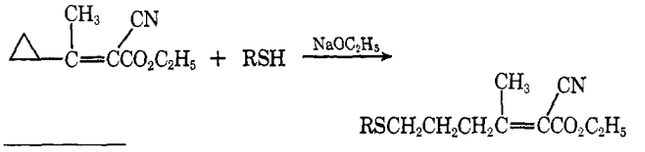


3

were prepared in good yield from methyl cyclopropyl ketone. Compound **1** was apparently a mixture of the geometrical isomers, a liquid and a crystalline solid, in approximately a 3:4 ratio. Both had the same infrared and near-infrared spectra and essentially the same elemental analysis. The liquid could be partially converted into the solid by heating at 140°. An equilibrium was apparently involved, for, if some of the solid was removed, more would form on further heating. The structure in which the methyl group is *cis* with respect to the nitrile group has been assigned to the solid isomer on the basis of nmr data. The methyl group singlet of the solid appears at the same point (δ 1.83) as observed in the spectrum of **2**, whereas in the liquid isomer this methyl group singlet appears at 1.73. The nitrile group thus apparently exerts a greater anisotropic deshielding effect than does the carboethoxy group.

Compound **3** also appeared to be a mixture of geometrical isomers. However, both were solids and separation was not so easily effected as in the case of **1**. The higher melting isomer was the major component of this mixture and was obtained pure by repeated recrystallizations. Attempts to prepare ethyl 2-carboethoxy-3-cyclopropyl-2-butenoate from methyl cyclopropyl ketone and diethyl malonate, using a variety of catalysts and reaction conditions, failed to give any of the desired product.

Reaction of **1** with benzenethiol and with 1-butanethiol in the presence of sodium ethoxide gave only one product in each case, resulting from exclusive 1,6 addition. The nmr spectra showed a complete absence of ethylenic protons in these products, indicating that the carbon–carbon double bond was entirely in a conjugated position. There were also no signals in the cyclopropyl hydrogen region of the spectra. (The complete nmr data are listed in the Experimental Section.)



(8) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenberg, *ibid.*, **63**, 3452 (1941).