furanone **1c** [bp 142–143 °C (8 mmHg)] and 5-phenyl-4,5-dihydro-2(3*H*)-furanone **1a** (mp 36–37 °C) were obtained from Aldrich; 1-phenyl-1-propyl acetate **2a** [bp 105 °C (16 mmHg)] and 1-(4-chlorophenyl)-1-propyl acetate **2b** [bp 135–137 °C (18 mmHg)] were prepared according to a known procedure;[12] 5-(4-chlorophenyl)-4,5-dihydro-2(3*H*)-furanone **1b**; (mp 43–44 °C) was prepared by the known method.[13] The lactones **1d–f** were identified on the basis of their IR (Perkin-Elmer E-177), $^1H$ or $^{13}C$ NMR (Varian A 90 or A 100 instrument), mass spectral data (GLC–MS system Varian MAT 112 S), and elemental analyses (C, ±0.2%; H, ±0.2%). All lactones isolated present an IR carbonyl stretching between 1775 and 1790 $cm^{-1}$.

**Synthesis of 5-Phenyl-5-methyl-4,5-dihydro-2(3*H*)-furanone (1d).** A solution of α-methylstyrene (0.02 mol) in acetic acid (7.5 mL) was added dropwise during 90 min to a well-stirred mixture of potassium peroxydisulfate (0.01 mol), potassium acetate (0.16 mol), and basic ferric acetate (0.005 mol) in acetic acid (42.5 mL) kept at 123 °C. The reaction mixture was stirred for an additional 30 min at 123 °C. Peroxydisulfate was found to be completely decomposed by iodometric titration of the insoluble inorganic salt after cooling, filtering, and washing with acetic acid. Carbon dioxide (0.41 g, 0.0093 mol) and methane (0.0091 g, 0.005 mol) were determined by trapping on KOH pellets and by GLC (molecular sieves (3 Å), 1 m, 100 °C), respectively. The reaction mixture was cooled, diluted with water, and extracted with ether. The organic extracts were combined and washed with 0.2 N HCl (100 mL) and with a saturated $Na_2CO_3$ solution (4 × 100 mL). The organic solution, after addition of methylbenzoate as internal standard, was analyzed by GLC on a column (2 m) of 10% UCC W 982 on Chromosorb W (80–100 mesh) with a Hewlett-Packard Model 575. The conversion of α-methylstyrene was 59% to give **1d** (47% yield, based on converted α-methylstyrene).

In a parallel experiment, on 10 times scale, the crude reaction product was chromatographed on silica gel (70–230 mesh), using an *n*-pentane–ether (80:20) mixture as eluent. **1d** (9.4 g, 0.053 mol, 45% yield) was isolated as an oil; an analytically pure sample was obtained by distillation in vacuo: bp 116–117 °C (1.8 mmHg) [lit.[14] bp 104–106 °C (0.1 mmHg)]; $^1H$ NMR ($CDCl_3$) δ 1.70 (s, 3 H), 2.47 (m, 4 H), 7.25 (m, 5 H); mass spectrum, *m/e* 161 (100), 43 (81), 105 (49), 121 (47), 77 (34), 51 (26), 56 (25), 176 ($M^{+\cdot}$, 7).

In a parallel experiment, carried out in the presence of $Cu(OAc)_2 \cdot H_2O$ (0.25 g, 0.00125 mol), **1d** was present only in a trace amount.

**Synthesis of 5-Phenyl-3,5-dimethyl-4,5-dihydro-2(3*H*)-furanone (1e).** The reaction was carried out as indicated in Table I. The **1e** was isolated by column chromatography on silica gel (pentane–ether eluent) and found to be a mixture of two diastereoisomers in the ratio 1:1; each diastereoisomer was isolated as pure during chromatography.

First diastereoisomer (to be eluted): bp 101–102 °C (1.4 mmHg); $^1H$ NMR ($CDCl_3$) δ 1.25 (d, 3 H, $J$ = 7.5 Hz), 1.74 (s, 3 H), 2–3 (m, 3 H), 7.25 (m, 5 H); $^{13}C$ NMR ($CDCl_3$) 84.59 (C5), 45.06 (C4), 35.11 (C3), 179.32 (C2), 30.36 ($CH_3$-C5), 14.82 ($CH_3$-C3); mass spectrum, *m/e* 105 (100), 174 (54), 43 (66), 77 (37), 42 (35), 131 (23), 121 (10), 190 ($M^{+\cdot}$, 3).

Second diastereoisomer (to be eluted): bp 104–106 °C (1.4 mmHg); $^1H$ NMR ($CDCl_3$) δ 1.25 (d, 3 H, $J$ = 7.5 Hz), 1.67 (s, 3 H), 2–3.2 (m, 3 H), 7.3 (m, 5 H); $^{13}C$ NMR ($CDCl_3$) 84.58 (C5), 44.14 (C4), 35.37 (C3), 178.99 (C2), 28.86 ($CH_3$-C5), 15.54 ($CH_3$-C3); mass spectrum, *m/e* 105 (100), 175 (54), 43 (66), 77 (37), 42 (35), 131 (23), 121 (18), 190 ($M^{+\cdot}$, 3).

**Synthesis of 5-Phenyl-3,3,5-trimethyl-4,5-dihydro-2-(3*H*)-furanone (1f).** Prepared as described in Table I, the lactone **1f** was isolated pure by column chromatography on silica gel (pentane–ether (9:1) eluent): bp 111–112 °C (1.5 mmHg); $^1H$ NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.35 (s, 3 H), 1.72 (s, 3 H), 2.2–2.7 (AB q, 1 H + 1 H, $J$ = 14.25 Hz), 7.3 (m, 5 H); $^{13}C$ NMR ($CDCl_3$) 83.54 (C5), 50.84 (C4), 40.96 (C3), 181.92 (C2), 26.85 ($CH_3$-C3), 26.07 ($CH_3$-C3), 32.12 ($CH_3$-C5); mass spectrum, *m/e* 105 (100), 43 (54), 189 (32), 145 (29), 77 (27), 56 (21), 121 (19), 204 ($M^{+\cdot}$, 3).

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**Oxidation of Acetic Acid in the Presence of Styrene and Quinoxaline.** A solution of styrene (0.02 mol) in acetic acid (7.5 mL) was added dropwise during 90 min to a stirred mixture of $K_2S_2O_8$ (0.01 mol), KOAc (0.16 mol), basic ferric acetate (0.005 mol), and quinoxaline (0.02 mol) in acetic acid (42.5 mL) at 123 °C. The reaction mixture was stirred for an additional 30 min at 123 °C. $CO_2$ (0.27 g, 0.0055 mol) and methane (0.021 g, 0.0012 mol) were determined. The reaction mixture was cooled, diluted with water, and extracted with ether as in the preparation of **1d**. From GLC data, the conversion of styrene was 36% to give **1a** (15% yield based on converted styrene) and **1b** (5% yield based on converted styrene). The conversion of quinoxaline was 26% to give 2-methylquinoxaline (57% yield based on converted quinoxaline) and dimethylquinoxaline (4% yield).

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**Registry No.** **1a**, 1008-76-0; **1b**, 18410-18-9; **1c**, 706-14-9; **1d**, 21303-80-0; **1e** (isomer 1), 77415-37-3; **1e** (isomer 2), 77415-38-4; **1f**, 77415-39-5; **2a**, 2114-29-6; **2b**, 77415-40-8; propionic acid, 79-09-4; isobutyric acid, 79-31-2; α-methylstyrene, 98-83-9; potassium peroxydisulfate, 7727-21-1; acetic acid, 64-19-7; styrene, 100-42-5; quinoxaline, 91-19-0; 2-methylquinoxaline, 7251-61-8; 2,3-dimethylquinoxaline, 2379-55-7.

## A Facile One-Step Synthesis of Diethyl [2-$^{13}$C]Malonate from Ethyl [2-$^{13}$C]Acetate

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Malonic acid and its esters, labeled with $^{13}C$ or $^{14}C$ at C-1 or C-2, have been used extensively in biosynthetic studies and as intermediates for the synthesis of more complex labeled compounds.[2] Malonic acid and its diethyl ester have usually been made from acetic acid, via bromo- or chloroacetic acid and cyanoacetate.[4] A 71% yield of diethyl [1-$^{13}$C]malonate was obtained from [1-$^{13}$C]acetic acid;[4b] however, the $^{13}C$ content of the product (40%) was less than that in the acetic acid (52%). This loss was attributed to exchange of the enriched acetic acid with unlabeled acetic anhydride used in the Hell–Volhard–Zellinsky bromination of acetic acid.

Rathke[5] obtained the lithium enolate of ethyl acetate by reaction of lithium bis(trimethylsilyl)amide with ethyl acetate in tetrahydrofuran at −78 °C. This salt is stable at low temperatures and reaction with aldehydes and ketones affords excellent yields of β-hydroxy esters.[5,6] We considered that diethyl malonate could be formed in one

(1) Contribution No. 177 from this laboratory.
(2) Diethyl 2-acetamidomalonate, produced by the reductive acetylation of diethyl 2-oximinomalonate, obtained by the nitrosation of diethyl malonate,[3] is especially useful for the synthesis of α-amino acids.
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(6) Braderer, H.; Knopp, D.; Daly, J. J. *Helv. Chim. Acta* **1977**, *60*, 1935–1941. These authors, apparently unaware of Rathke's publication,[5a] prepared the ethyl lithioacetate by the same method and used it for the synthesis of a β-hydroxy ester which was subsequently converted to the hasubanane ring system.

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step by reaction of lithium ethyl acetate with ethyl carbonate or ethyl chloroformate. Diethyl carbonate failed to react at the low temperature needed to prevent self-condensation of the ethyl lithioacetate. However reaction between ethyl chloroformate and the ethyl lithioacetate, generated from ethyl acetate by the use of 1 equiv of lithium bis(trimethylsilyl)amide, afforded a 48% yield of diethyl malonate. We reasoned that the poor yield was due to protonation of the ethyl lithioacetate by the product, diethyl malonate. This decomposition of the ethyl lithioacetate was avoided by the use of slightly more than 2 equiv of the lithium bis(trimethylsilyl)amide, and excellent yields (86–92%) of diethyl malonate were obtained. The yield was estimated by GLC of the crude product which was contaminated with some bis(trimethylsilyl) ether. This impurity was not deleterious in subsequent conversion of the diethyl malonate to diethyl 2-acetamidomalonate.[2] Poorer yields of diethyl malonate were obtained when the ethyl lithioacetate was generated with lithium diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide.[7]

## Experimental Section

**Diethyl [2-$^{13}$C]Malonate.** *n*-Butyllithium (15 mL of a 2.1 M solution in hexane, 31.5 mmol) was added slowly to a solution of bis(trimethylsilyl)amine (4.04 g, 40 mmol) in dry THF (30 mL), stirred magnetically, in a $N_2$ atmosphere, cooled to −65 °C (internal thermometer). The solution was warmed to 20 °C during 20 min and then cooled to −72 °C in a dry ice–methanol bath. Ethyl [2-$^{13}$C]acetate (1.353 g, 15.2 mmol, 92% $^{13}$C) dissolved in THF (3.5 mL) was added to the reaction mixture during 7 min by means of a syringe. An additional quantity of THF (3.5 mL) was used to rinse out the syringe and flask which had contained the labeled ethyl acetate. The solution was stirred for 30 min at −72 to −75 °C and then freshly distilled ethyl chloroformate (1.65 g, 15.2 mmol) was added by means of a syringe, keeping the temperature below −55 °C. After the reaction mixture was stirred for another 2 h at −75 °C, 6 M HCl (4 mL) was added, followed by water (20 mL) and ether (100 mL). The ether layer was separated and the aqueous solution extracted with additional ether (50 mL). The combined ether extracts were washed successively with 3 M HCl (20 mL), water (50 mL), and 5% aqueous $NaHCO_3$ (50 mL). The HCl and water washes were combined and extracted with ether (2 × 20 mL). These ether extracts were washed with 5% aqueous $NaHCO_3$ and then combined with the original ether extract. Evaporation (50 °C, 12 mm) of the dried ($Na_2SO_4$) extract yielded crude diethyl [2-$^{13}$C]malonate (2.430 g). Analysis of this material by GLC[8] indicated a purity of 86.8%; thus the actual yield of diethyl malonate was 2.109 g (86%). Proton NMR indicated that the $^{13}$C enrichment of the product was essentially the same as the starting ethyl [2-$^{13}$C]acetate: $^1$H NMR (80 MHz, FT, $CDCl_3$) $\delta$ 4.18 (4 H, q, $OCH_2CH_3$, $^3J_{H,H}$ = 7.1 Hz), 3.32 (1.84 H, d, C(O)$^{13}$C$H_2$C(O), $^1J_{C,H}$ = 132 Hz), 3.32 (0.16 H, s, C(O)C$H_2$C(O), 1.27 (6 H, t, $OCH_2CH_3$, $^3J_{H,H}$ = 7.1 Hz); $^{13}$C NMR (25.2 MHz, FT, $^1$H decoupled, $CDCl_3$) $\delta$ 166.6 (d, C(O)$CH_2$, $^1J_{C,C}$ = 59.2 Hz, singlet from unenriched material not discernible from background), 61.5 (s, $OCH_2CH_3$), 41.7 (t, C(O)$CH_2$C(O), $^1J_{C,C}$ = 59.2 Hz), 14.1 (s, $OCH_2CH_3$).

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**Registry No.** Ethyl [2-$^{13}$C]acetate, 58735-82-3; ethyl chloroformate, 541-41-3; diethyl [2-$^{13}$C]malonate, 67035-94-3.

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# Folate Analogues. 17. Synthesis of Pteroic Acid and 4-Amino-4-deoxypteroic Acid[1]

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In connection with our studies concerning the development of synthetic substrates[2] of the enzyme dihydrofolate reductase (EC 1.5.1.3) it occurred to us that the protected bromomethyl ketone **6** would be a useful intermediate for the construction of certain classical folate analogues such as 7,8-dihydro-8-oxafolic acid[3] and 7,8-dihydro-8-thiofolic acid.[4] In addition, the protected amino ketone **11** derived from **6** appeared to be of potential value for alternate syntheses[5,6] of the biologically relevant[7-9] pteroic acids **1**, **2**, and **3**, based on the well-known Boon–Leigh strategy.[10,11] In this paper we describe the preparation of these ketones and their conversions to **1** and **3** (Chart I).

Fusion of 1 equiv of bromoacetic acid with 1 equiv of ethyl *p*-aminobenzoate resulted in the formation of *N*-(*p*-carbethoxyphenyl)glycine (**4**) which, upon treatment with trifluoroacetic anhydride[12] and aqueous workup, gave the *N*-trifluoroacetyl derivative **5**. This compound was converted to the corresponding acid chloride with the use of thionyl chloride and was subsequently elaborated to the diazo ketone **5b** by treatment with diazomethane. Gaseous HBr or HCl converted an ethereal solution of **5b** to the corresponding bromomethyl ketone **6** or chloromethyl ketone **7** in good yield.[1]

Conversion of the bromomethyl ketone to the azidomethyl ketone **8** was accomplished by treating **6** with sodium azide under a carefully controlled set of conditions in anhydrous acetone.[1] The carbonyl group of the crystalline azide **8** was protected as the dimethyl ketal **9**, using methanol and $H_2SO_4$. Hydrolysis of **9** with NaOH also resulted in the removal of the protective group and gave an excellent yield of **10**. Hydrogenation of **10** in MeOH using 5% palladium on carbon gave the protectd $\alpha$-amino

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