Reactions of Methoxyvinyllithium. Synthesis and Rearrangement of 4-Hydroxyisopyrazoles

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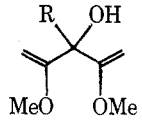
Reaction of methoxyvinyllithium (MVL) with aliphatic and aromatic esters gives, via an isolable divinyl ether intermediate, 3-hydroxy-2,4-pentanediones, which with hydrazine yield the previously unknown 4-hydroxyisopyrazoles. The stereochemistry of their facile thermal rearrangement to 2-pyrazolin-4-ones has been studied.

Recently we described the convenient acyl anion equivalent methoxyvinyllithium (MVL) and some of its reactions.[1-3] In the course of a study of the reactions of MVL with esters we hydrolyzed the initial adducts **1** to the hydroxy diones, as **2**,[1] and then treated these substances with hydrazine in alcohol



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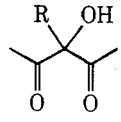

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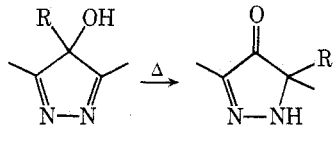
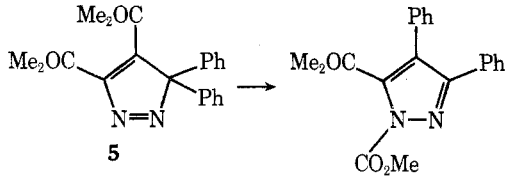
to furnish the previously unknown 4-hydroxyisopyrazoles **3**. These isopyrazoles **3** were thermally unstable, undergoing a smooth conversion to the 2-pyrazolin-4-ones **4** (cf. Table I)



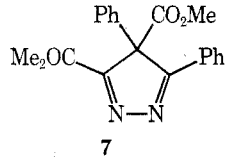
3 **4**

R = alkyl, phenyl

at relatively low temperature (ca. 100 °C). This reaction is undoubtedly related to the van Alphen–Hüttel rearrangement of geminally disubstituted pyrazolenines.[4-6] Thus van Alphen observed the conversion of the pyrazolenine **5** to a substance thought to be **6** in acetic acid at 100 °C.[4] However, it was subsequently shown that this was in fact the isopyrazole **7**



5 **6**



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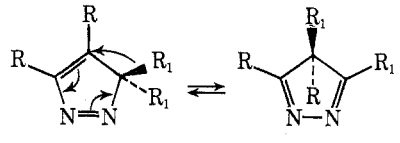
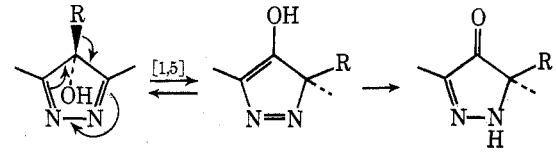
which could also be obtained by simply heating **5**.[6] These later authors[6] described this reaction as a thermal [1,5] sigmatropic change, which in the suprafacial mode should proceed with retention of configuration of the migrating group,[7] Scheme I. A similar [1,5]-sigmatropic shift is reasonable for the purely thermal rearrangement of the 4-hydroxyisopyrazoles **3**, which

Scheme I

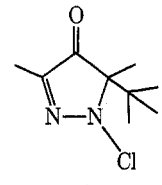


followed by a tautomerization provides the 2-pyrazolin-4-ones, Scheme II. In order to examine the stereochemistry involved

Scheme II



in this [1,5] shift we required a simple degradation of the rearrangement products and to this end examined some possible routes. An attempted ring cleavage reaction on the *N*-chloro derivative **8**, generated by reaction with *tert*-butyl hypochlorite (−78 °C), gave, by action of ethanolic sodium ethoxide, the ether **9**, presumably by way of the dehydropyrazole **10**. Lithium aluminum hydride reduction of the pyrazolone



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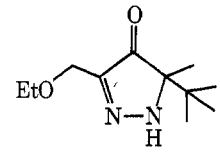

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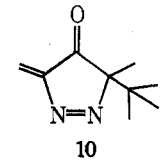

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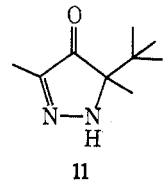
11 took an unexpected course, giving cleanly the dealkylated pyrazole **12** and presumably isobutylene. A reasonable precursor of **12** might be the deoxygenated isopyrazole **13** as its



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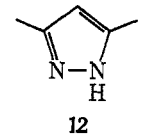

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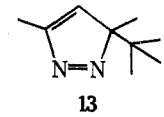

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aluminum complex. This same reductive dealkylation was observed in the *sec*-butyl substituted analogue of pyrazolone **11**. Eventually we were successful in establishing a stereochemical cycle which related the stereochemistry of the purely thermal [1,5]-sigmatropic shift to a [1,2] shift of the type characteristic of alkyl migration to an electron-deficient terminus. This is described in Scheme III. Thus the optically active isopyrazole **14**, obtained from (+)-methyl α-methylbutyrate, was thermally rearranged (110 °C, 3 min) to the pyrazolinone **15** and then converted, sequentially, by methylation and reduction to the stereoisomeric mixture of alcohols **19**, which upon treatment with mineral acid underwent a [1,2] shift to the pyrazole **18**. This same pyrazole was obtained from **14** by a reduction and methylation sequence, Scheme III. Care was taken to avoid any stereochemical fractionation at every stage in this cycle. The results are indicated in Table II.

These results prove that the stereochemistry of the thermal reaction [1,5] is identical with that of the acid-catalyzed process [1,2]. If the reasonable assumption is made that this latter process is of the general class of [1,2] rearrangements known

Table I

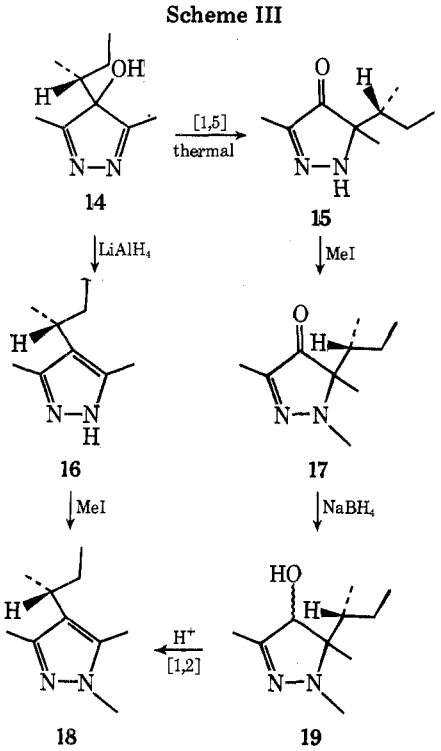
Ester	Enol ether 1 yield,[a] bp	Hydroxy dione 2 yield, bp, mp	Isopyrazole 3 yield, mp	2-Pyrazolin-4-one 4 yield, bp or mp
Methyl valerate (A)	82%, 57.5–58.0 °C (0.01 mm)	83%, 71–74.5 °C (4.5 mm)	51%, 93.5–95 °C	87%, 80 °C (0.07 mm)
(±)-Methyl α-methylbutyrate (B)	93%	62%, 93–96 °C (21 mm)	51%, 91.5–93 °C	89%, 85–86 °C (2.0 mm)
Methyl pivalate (C)	95%	52%, mp 50–52 °C	49%,[b] 83–93 °C	39%, mp 91–94 °C
Methyl benzoate (D)	75%, 82–85 °C (0.02 mm)	64%, 65–67 °C (0.17 mm)	57%, 162–163 °C	62%, mp 86–88 °C
(+)-Methyl α-methylbutyrate (E)	88%	66%, 91–92 °C (20 mm)	93%, 99–100 °C	92%, mp 61–62.5 °C

[a] All yields are for isolated purified substances. [b] The actual conversion yield in this case is low owing to loss of product by rearrangement.

Table II

1.	Pyrazole 18 from [1,5] and [1,2] pathway	$[\alpha]^{28}D$ +20.2° (c 4.35, $CHCl_3$) Picrate, mp 109.5–110.5 °C
2.	Pyrazole 18 from 14 via 16	$[\alpha]^{29}D$ +19.9° (c 6.47, $CHCl_3$) Picrate, mp 109.5–110 °C

Scheme III



to proceed with retention of the migrating group[8] then it follows that the thermal path [1,5] **14** to **15** also proceeds with retention. Furthermore, we demonstrated the essential thermal nature of this [1,5] rearrangement, **14** to **15**, by observing no change in the rate of this conversion (NMR) in pyridine upon addition of trifluoroacetic acid. An acid-catalyzed process was thereby eliminated.

In summary, we have found a convenient route to certain 4-hydroxyisopyrazoles and studied the stereochemistry of their thermal rearrangement to 2-pyrazolin-4-ones. This stereochemistry of the migrating alkyl group has been shown to be identical with that of an acid-catalyzed [1,2] shift. It follows that the thermal rearrangement of 4-hydroxyisopyrazoles to 2-pyrazolin-4-ones proceeds with retention of configuration in the migrating group.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Midwest Microlabs Inc., Indianapolis, Ind. Ir spectra were recorded on a Perkin-Elmer Model 700 spectrophotometer. NMR spectra were recorded on a Varian Associates T-60 spectrometer or a Hitachi Perkin-Elmer R-22B instrument. Silica gel for column chromatography was Davison Chemicals grade 950 (60–200 mesh) or Merck silica gel 60, no. 7734.

3-*n*-Butyl-3-hydroxy-2,4-pentanedione (2a). Methyl valerate (9.27 g, 80 mmol) was added dropwise under nitrogen to a cold (−65 °C) solution of MVL (2 equiv) in THF–pentane. After stirring for 0.5 h at −65 °C and 1 h at room temperature, 10% aqueous ammonium chloride (50 ml) was cautiously added dropwise to the cooled (0 °C) solution. The aqueous phase was extracted with ether, and the combined organic layers washed with brine, dried ($MgSO_4$), and evaporated to leave bis enol ether **1a** (15.7 g, 98%). Distillation provided **1a** 13.2 g (82%) as a colorless liquid: bp 57.5–58.0 °C (0.01 mm); ir (film) 3700–3200, 1655, 1625 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 0.67–2.06 (m, 9 H), 2.84 (s, 1 H, exchangeable with D_2O), 3.57 (s, 6 H), 4.12 and 4.38 (AB quartet, 4 H, J_{AB} = 2.5 Hz).

Enol ether **1a** (7.0 g, 35 mmol) was stirred with methanol (40 ml) and 0.1 N HCl (20 ml) for 1.5 h, then diluted with brine (50 ml) and extracted with ether (4 × 30 ml). The combined extracts were washed with water (30 ml), dried ($MgSO_4$), and concentrated. Distillation gave **2a,** 4.97 g (83%), as a colorless liquid: bp 71–74.5 °C (4.5 mm); ir (film) 3550–3250, 1705 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 0.7–1.6 (m, 7 H), 1.8–2.2 (m, 2 H), 2.25 (s, 6 H), 4.68 (s, 1 H, exchangeable with D_2O).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.37. Found: C, 63.4; H, 9.42.

4-*n*-Butyl-3,5-dimethyl-4-hydroxy-4*H*-pyrazole (3a). To a solution of **2a** (860 mg, 5 mmol) in absolute ethanol (3 ml) at 0 °C was added hydrazine hydrate (99–100%, 262 mg, 5.15 mmol) with stirring. After 0.5 h at 0 °C, the solution was concentrated at 20 °C under reduced pressure to give a clear oil. Benzene (5 ml) was added and removed under reduced pressure. Repetition of this three times gave a waxy solid, which was recrystallized from hexane–dichloromethane to provide white needles of **3a,** 392 mg (47%): mp 93.5–95 °C; NMR ($CDCl_3$) δ 0.83 (br t, 3 H), 1.0–2.0 (m, 6 H), 2.10 (s, 6 H), 6.9 (br s, 1 H). This compound obtained as described was stable in the solid state for several days when stored under nitrogen in the freezer (−20 °C); however, with traces of acid or moisture or when stored at room temperature, decomposition was rapid.

5-*n*-Butyl-3,5-dimethyl-2-pyrazolin-4-one (4a). A sample of **3a** (259 mg) was heated in the melt (bath 120 °C) under nitrogen for 10 min and then cooled. The product was transferred (in 1 ml of pentane) to a microdistillation apparatus and distilled at an oven temperature of 80 °C (0.07 mm) to give a mobile yellow liquid, 255 mg (87%), identified as **4a** by its spectral properties: ir (film) 3300, 1685 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 0.90 (br t, 3 H), 1.0–1.9 (m, 9 H, a 3 H singlet was visible at δ 1.30), 2.06 (s, 3 H), 6.55 (br s, 1 H); uv (EtOH) λ_{max} 330 nm (ε 4800) and 204 (3000), shifted to λ_{max} 357 nm (ε 7000), 335 (6640), and 211 (21 200) upon addition of base (1 N NaOH).

(±)-3-*sec*-Butyl-3-hydroxy-2,4-pentanedione (2b). The bis enol ether **1b** was prepared analogously to **1a** in 93% crude yield, using *dl*-methyl α-methylbutyrate (7.8 g, 67 mmol) as the electrophile: ir (film) 3540, 1650, 1620 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 2.0–0.65 (complex multiplet, 9 H), 2.87 (br s, 1 H), 3.50 (s, 6 H), 4.37, 4.29 (AB quartet, J = 3 Hz, 4 H).

The crude enol ether **1b** was hydrolyzed using aqueous methanolic HCl, and after normal workup gave **2b,** 9.43 g (82%). Distillation afforded 7.15 g (62% based on starting ester) as a water-white liquid: bp 93–96 °C (21 mm); ir (film) 3435, 1705 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 4.60 (s, 1 H, exchangeable with D_2O), 2.67–2.26 (m, 1 H), 2.23 (s, 6 H), 1.34–0.76 (complex m, 8 H); mass spectrum (70 eV) *m/e* 172 (parent ion).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.37. Found: C, 63.1; H, 9.63.

(±)-4-*sec*-Butyl-3,5-dimethyl-4-hydroxy-4*H*-pyrazole (3b). Hydrazine hydrate (99–100%, 141 μl, 2.91 mmol) was added dropwise to a cold (−15 °C bath) solution of the hydroxy diketone (500 mg, 2.91 mmol) in absolute MeOH (~750 μl). The reaction mixture was stirred at −15 °C for 0.5 h, and then rotary evaporated (0 °C, 0.2 mm). The white solid remaining was triturated (2 × 4 ml) with pentane to leave white crystalline **3b**. Recrystallization gave white needles, 250 mg (51%): mp 91.5–93 °C; ir (film) 3370–2800, 1601 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 6.9–6.5 (br s, 1 H, exchanges with D_2O), 2.12 (s, 6 H), 1.82–1.45 (m, 1 H), 1.15–0.65 (complex m, 8 H); uv (EtOH) 232 nm (ε 1300).

(±)-5-*sec*-Butyl-3,5-dimethyl-2-pyrazolin-4-one (4b). Thermal reorganization was effected by heating under nitrogen **3b** (1.76 g, 10.5 mmol) in an oil bath at 110 °C for 3 min. Distillation through a Vigreux column (10 cm) gave **4b**, 1.57 g (89%): bp 85–86 °C (1.8–1.9 mm); ir (film) 3320, 1700, 1685 cm^{-1}. The diastereomeric relationships of **4b** may be inferred from the 90-MHz NMR ($CDCl_3$): δ 6.78–6.49 (br s, 1 H, exchangeable), 2.02 (s, 3 H), 1.86–1.45 (complex m, 1 H), 1.27, 1.24 (two singlets diastereomerically related, 3 H total), 1.24–0.73 (complex m, 5 H), 1.01 (d, 3 H, J = 7 Hz); uv (EtOH) λ_{max} 330 nm (ε 3960), 202 (ε 2080), shifted to 356 (5140), 212 (>20 000) upon addition of OH; mass spectrum m/e 168 (parent ion).

3-*tert*-Butyl-3-hydroxy-2,4-pentanedione (2c). The bis enol ether **1c** was obtained crude (20.3 g, 100%) in greater than 95% purity, using methyl pivalate (13.05 ml, 100 mmol) as the electrophile. Hydrolysis was effected with 0.02 N aqueous methanolic HCl to leave after normal workup yellow, crystalline diketone, which was recrystallized from methanol to afford colorless needles of **2c**, 7.93 g. Concentration and cooling of the mother liquors gave additional needles, 1.05 g (total 8.98 g, 52%, based on starting ester): mp 50–52 °C; ir ($CHCl_3$) 3420, 1705 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 4.78 (s, 1 H, exchanges with D_2O), 2.32 (s, 6 H), 1.07 (s, 9 H); mass spectrum m/e 172 (parent ion). The analytical sample was prepared by two consecutive sublimations at ambient temperature (0.5 mm).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.37. Found: C, 62.9; H, 9.72.

4-*tert*-Butyl-3,5-dimethyl-4-hydroxy-4*H*-pyrazole (3c). Hydrazine hydrate (99–100% 432 μl, 8.90 mmol) was added dropwise to a cold (0 °C bath) solution of the diketone **2c** (1.53 g, 8.90 mmol) in absolute MeOH (18 ml). The mixture was stirred at 0 °C for 15 min, and 25 °C for 0.5 h, followed by evaporation at 25 °C (2 mm) to leave a waxy yellow solid. Trituration with pentane left **3c**, 740 mg (49%), as white plates: mp 83–93 °C; 90-MHz NMR ($CDCl_3$) δ 6.89–6.67 (br s, 1 H, exchangeable with D_2O), 2.14 (s, 6 H), 1.00 (s, 9 H). A low yield for **3c** results from facile rearrangement to **4c** during isolation.

5-*tert*-Butyl-3,5-dimethyl-2-pyrazolin-4-one (4c). Hydrazine hydrate (99–100%, 288 mg, 5.76 mmol) in MeOH (1 ml) was added dropwise to a cold (0 °C bath) solution of the diketone **2c** (992 mg, 5.76 mmol) in MeOH (8 ml). The solution was stirred at 0 °C for 15 min and 0.5 h at room temperature. Evaporation left a waxy solid which by NMR was partially rearranged material. Thermal reorganization was accomplished upon heating under nitrogen (120 °C bath) for 2 min. On cooling crystalline **4c** (880 mg) separated. **4c** was obtained as beautiful needles, mp 91–94 °C, 457 mg (39%), after three sublimations (100 °C, 760 mm). Starting diketone **2c** tends to cosublime with **4c** leading to difficulty in purification: ir ($CHCl_3$) 3380, 1705, 1685 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 6.70–6.39 (br s, 1 H, exchanges with D_2O), 2.03 (s, 3 H), 1.26 (s, 3 H), 1.00 (s, 9 H); uv (EtOH) λ_{max} 330 nm (ε 3970).

3-Hydroxy-3-phenylpentane-2,4-dione (2d). The bis enol ether **1d** was obtained from methyl benzoate (6.8 g, 50 mmol) as a colorless oil, 8.2 g (74.5%), after distillation (bp 82–85 °C, 0.02 mm) of the crude material. Enol ether **1d** formed colorless prisms on standing: mp 55.5–59.5 °C; ir ($CHCl_3$) 3550, 1665, 1635 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 3.77 (s, 1 H, exchanges with D_2O), 3.60 (s, 6 H), 4.25 [s, 4 H, the vinyl protons appeared as an AB quartet (4 H), J_{AB} = 2.5 Hz at 4.12, 4.27 when the spectrum was determined in CCl_4], 7.24–7.70 (m, 4 H).

An analytical sample was prepared by recrystallization from hexane, mp 60.5–61 °C.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.32. Found: C, 71.0; H, 7.41.

Hydroxy dione **2d** was obtained in 64% (overall from methyl benzoate) isolated yield by direct hydrolysis (methanol, 0.1 N HCl, 3:1) of crude enol ether **1d**. Alternatively hydrolysis under the same conditions of purified **1d** gave **2d** in 80–85% yield: bp 65–67 °C (0.17 mm); ir (film) 3400, 1710 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 2.30 (s, 6 H), 5.30 (s, 1 H, exchangeable with D_2O), 7.27–7.64 (m, 5 H).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.7; H, 6.29. Found: C, 69.3; H, 6.60.

This compound was a colorless liquid when freshly distilled, but rapidly developed a yellow color on storage with no change in spectral properties.

3,5-Dimethyl-4-hydroxy-4-phenyl-4*H*-pyrazole (3d). To a cold (10 °C) solution of **2d** (9.60 g, 50 mmol) in absolute ethanol (65 ml) was added dropwise hydrazine hydrate (99–100%, 2.5 g, 50 mmol) with stirring. A white precipitate appeared which after 0.5 h at 0 °C was collected and washed with a little cold ethanol to give crude **3d**, 8.35 g, mp 158–159 °C. Recrystallization from benzene containing a trace of ethanol (2%, 120 ml) provided colorless needles, 5.35 g (57%), of **3d**: mp 162–163 °C; ir ($CHCl_3$) 3500–2900, 1603 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 2.03 (s, 6 H), 7.33 (br s, 5 H), 7.73 (br s, 1 H, exchangeable); NMR (Me_2SO-d_6) δ 1.83 (s, 6 H), 6.80 (br s, 1 H), 6.95–7.50 (m, 5 H); mass spectrum (70 eV) m/e 188 (parent ion); uv (EtOH) λ_{max} 212 nm (ε 4000) with broad shoulder.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.42. Found: C, 69.7; H, 6.54.

3,5-Dimethyl-5-phenyl-2-pyrazolin-4-one (4d). Isopyrazole **3d** (1.1 g) was heated under nitrogen in the melt (175 °C bath) for 60 s. Upon cooling, yellow needles were obtained, mp 84–86 °. Recrystallization from hexane–dichloromethane gave **4d** as pale yellow prisms, 680 mg (62%): mp 86–88 °C; ir (film) 3300, 1710, 1690 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 1.67 (s, 3 H), 2.06 (s, 3 H), 6.9 (br s, 1 H), 7.35 (s, 5 H); uv (EtOH) λ_{max} 331 nm (ε 5100), 207 (10 100) shifted to 366 (7130), 350 (6290), and 211 (16 900) upon addition of base (1 N NaOH).

(+)-Methyl α-Methylbutyrate. Ethereal diazomethane was added in portions to (+)-methyl-α-methylbutyric acid[9] (5.23 g, 51 mmol) in Et_2O (75 ml), until the evolution of nitrogen had ceased. The ethereal solution was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated at room temperature to leave (+)-methyl α-methylbutyrate. Distillation afforded 3.43 g (58%), bp 114–117 °C, $[\alpha]^{25}D$ +21.04° (c 5.5, $CHCl_3$) [lit.[10] bp 108–109 °C (751 mm) $[\alpha]^{22}D$ +23.2° (neat)].

(+)-3-*sec*-Butyl-3-hydroxy-2,4-pentanedione (2e). The bis enol ether **1e**, 4.9 g (88% crude), was obtained from (+)-methyl α-methylbutyrate (3.24 g, 28 mmol). Hydrolysis of the enol ether was effected as above for **1b** to give **2e**, 2.68 g (66% based on starting ester), after distillation, bp 91–92 °C (20 mm), $[\alpha]^{26}D$ +16.7° (c 15.5, $CHCl_3$).

(−)-4-*sec*-Butyl-3,4-dimethyl-4-hydroxy-4*H*-pyrazole (3e). The optically active isopyrazole was prepared in the same manner as in the racemic series, using **2e** (2.44 g, 14.2 mmol) and hydrazine hydrate (689 μl, 14.2 mmol) to give **3e** upon trituration, 2.21 g (93%): mp 99–100 °C: $[\alpha]^{25}D$ −18.4° (c 31.4, $CHCl_3$); ir ($CHCl_3$) 3500–3650, 1601 cm^{-1}; 60-MHz NMR ($CDCl_3$) δ 2.12 (s, 6 H). 1.78–1.35 (complex m, 1 H), 1.12–0.58 (complex m, 8 H).

(−)-5-*sec*-Butyl-3,5-dimethyl-2-pyrazolin-4-one (4e). Rearrangement of **3e** (1.36 g, 8.1 mmol) was effected as in the racemic series to give **4e**, 1.25 g (92%), as a yellow liquid after distillation. The pyrazolin-4-one solidifies on standing and may be sublimed at room temperature (0.1 mm), giving white needles, mp 61–62.5 °C, $[\alpha]^{25}D$ −38.5° (c 79.4, $CHCl_3$).

5-*tert*-Butyl-3-ethoxymethyl-5-methyl-2-pyrazolin-4-one (9). *tert*-Butyl hypochlorite (228 μl, 1.9 mmol) was added to a cold (−78 °C bath) solution of the pyrazolone **4c** (320 mg, 1.90 mmol) in anhydrous ether (20 ml). The clear solution became cloudy and was stirred for 0.5 h at −78 °C, warmed to room temperature, and stirred for 2 h. Evaporation left a yellow oil: ir (film) 1760, 1380 cm^{-1}; 60-MHz NMR ($CDCl_3$) 1.96 (s, 3 H), 1.55 (s, 3 H), 1.20 (s, 9 H).

The yellow oil was stirred at room temperature under nitrogen with excess sodium ethoxide in ethanol (50 ml) for 2 h. Acidification and extraction with Et_2O gave upon evaporation of the dried solution a yellow oil, 80 mg.

Preparative TLC (elution with 30% EtOAc in hexane) gave a fluorescent band. Extraction with chloroform and evaporation gave yellow crystalline **9**: mp 88–89 °C; 90-MHz NMR ($CDCl_3$) δ 7.07–6.82 (br s, 1 H, exchangeable with D_2O), 4.26 (s, 2 H), 3.54 (q, 2 H, J = 7 Hz), 1.33–0.88 (complex m, 15 H with a 9 H s visible at 0.98); ir ($CHCl_3$) 3400, 1705, 1685 cm^{-1}.

3,5-Dimethylpyrazole 12 from $LiAlH_4$ Reduction. A solution of the *sec*-butylpyrazolinone **4b** (500 mg, 2.98 mmol) in THF (8 ml) was refluxed under nitrogen with excess $LiAlH_4$ (226 mg, 5.95 mmol) for 12 h and then quenched by careful sequential addition of H_2O (23 μl), 10% KOH (700 μl), and H_2O (1 ml). The white precipitated lithium salts were filtered, and the resulting organic solution washed with brine, dried (Na_2SO_4), and evaporated. The resultant yellow oil was chromatographed on silica gel [elution with PhH/EtOAc (1:1)] to give 3,5 dimethylpyrazole as white needles, 160 mg (50%), mp 100–102 °C (lit.[11] 107–108 °C). The *tert*-butylpyrazolinone **4c** similarly gave

3,5-dimethylpyrazole **12** in 60% yield, mp 99–101 °C after chromatography.

(+)-4-*sec*-Butyl-3,5-dimethylpyrazole (16). A suspension of hydroxyisopyrazole **3e** (752 mg, 4.48 mmol) and excess $LiAlH_4$ (540 mg, 14.2 mmol) in ether (100 ml) was stirred at room temperature under nitrogen for 9 h and then quenched by sequential dropwise addition of H_2O (0.5 ml), 10% aqueous sodium hydroxide (10.5 ml), and H_2O (1.5 ml). Filtration, washing the ethereal filtrate with brine, drying (Na_2SO_4), and evaporation left a clear, colorless liquid, 546 mg (80% crude). The compound solidified on standing to form needle clusters: mp 38–39 °C; ir (film) 3600–2800, 1585, 1465, 1390 cm^{-1}; uv (EtOH) λ_{max} 224 nm (ϵ 3410); 90-MHz NMR ($CDCl_3$) δ 7.28–6.93 (br s, 1 H, exchanges), 2.76–2.27 (complex m, 1 H), 2.21 (s, 6 H), 1.78–1.33 (m, 2 H), 1.23 (d, 3 H, J = 7 Hz), 0.82 (t, 3 H, J = 7 Hz); $[\alpha]^{25}D$ +19.80° (c 4.21, $CHCl_3$); mol wt 152.13163 (calcd for $C_9H_{16}N_2$, 152.13134).

(+)-4-*sec*-Butyl-1,3,5-trimethylpyrazole (18). Washed NaH (86 mg, 3.59 mmol, prepared by repeated washing and centrifugation of a mineral oil suspension with ether) suspended in THF (20 ml) was added via syringe to a solution of the optically active pyrazole **16** (546 mg, 3.59 mmol) in THF (15 ml). The mixture was refluxed under nitrogen overnight, cooled to room temperature, and treated with MeI (223 μl, 3.59 mmol) with stirring at room temperature for 4 h. The precipitated NaI was filtered; the filtrate washed with ether, and the combined organics were diluted with chloroform, washed with brine, dried (Na_2SO_4), and evaporated to leave 349 mg of crude **18**.

Preparative TLC elution with chloroform gave a yellow band at R_f ~0.5. Extraction with chloroform and evaporation gave **18**, 321 mg (54%), as a pale yellow liquid: ir (film) 1570, 1470, 1390, 1310, 1010 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 3.67 (s, 3 H), 2.71–2.27 (m, 1 H), 1.77–1.40 (m, 2 H), 1.20 (d, 3 H, J = 7 Hz), 0.82 (t, 3 H, J = 7 Hz); uv (EtOH) λ_{max} 230 nm (ϵ 4360); $[\alpha]^{29}D$ + 19.9° (c 64.7, $CHCl_3$); mol wt 166.14557 (calcd for $C_{10}H_{18}N_2$, 166.14699).

18 also forms a picrate as beautiful yellow needles from ethanol, mp 109.5–110 °C.

(−)-5-*sec*-Butyl-1,3,5-trimethyl-2-pyrazolin-4-one (17). A suspension of washed KH (289 mg, 7.23 mmol, prepared by repeated washing and centrifugation of KH in oil suspension with ether) in THF (23 ml) was added via syringe under nitrogen to a solution of the pyrazolin-4-one **1e** (1.17 g, 6.96 mmol) in THF (25 ml) at room temperature. When the visible hydrogen evolution had ceased, the reaction mixture was brought to reflux for 20 min, cooled to room temperature, and treated with excess MeI (1.73 ml, 27.8 mmol) for 4 h. Filtration of the potassium iodide and evaporation left a yellow oil (1.22 g) which showed 60% starting material by NMR. The mixture was refluxed further with additional KH (263 mg, 6.6 mmol) for 1 h, treated with MeI (1.64 ml, 21 mmol), and stirred for 5 h at room temperature. Filtration of the precipitated potassium iodide and evaporation left 1.18 g of crude **17**. A solution of crude **17** in dichloromethane was washed with brine, dried ($MgSO_4$), and evaporated.

Distillation gave a fraction, 897 mg, bp 84–97 °C (2.2 mm), which was redistilled to give **17**, 403 mg (32%): bp 81–84 °C (2.1–2.4 mm); ir (film) 1700, 1682 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 3.23 (s, 3 H), 1.98 (s, 3 H), 1.23 (s, 3 H), 1.86–0.82 (complex m, 9 H); uv (EtOH) λ_{max} 367 nm (ϵ 5740) with large end absorption ~200 nm; $[\alpha]^{25}D$ −16.6° (c 4.40, $CHCl_3$). Racemic **17** was prepared similarly in 51% yield: bp 78–79.5 °C (2.5 mm); mass spectrum m/e 182 (parent ion).

(+)-5-*sec*-Butyl-4-hydroxy-1,3,5-trimethylpyrazoline (19). The methylated pyrazolin-4-one **17** (403 mg, 2.21 mmol) and sodium borohydride (85 mg, 2.21 mmol) were refluxed in ethanol (15 ml) for 2 h. Evaporation of the ethanol left a white solid which was partitioned between H_2O and ether. The aqueous phase was extracted with ether, and the combined ether extracts washed with brine, dried (Na_2SO_4), and evaporated to leave 326 mg of a colorless liquid. Preparative thin layer chromatography (elution with ethyl acetate) gave **19** as a clear oil, 245 mg (60%): $[\alpha]^{28}D$ +5.14° (c 6.17 $CHCl_3$); ir (film) 3650–2800, 1625, 1475, 1385, 1139, 1078 cm^{-1}. The presence of a stereoisomeric mixture resulting from reduction at either face of the molecule may be inferred from the NMR spectrum: 90-MHz NMR ($CDCl_3$) δ 4.56, 4.06 (two broad singlets, 1 H total), 2.72, 2.67 (two singlets, 3 H total, the signal at 2.72 show a 2-Hz long-range coupling to the carbinol proton), 2.40 (br s, exchangeable), 2.01, 1.91 (two singlets, 3 H total, the signal at 1.91 shows a long-range 2-Hz coupling to the carbinol proton), 1.91–0.81 (complex multiplet, 12 H).

(+)-4-*sec*-Butyl-1,3,5-trimethylpyrazole (18). Optically active **19** (190 mg, 1.03 mmol) in EtOH (5 ml) was refluxed with 6 drops of concentrated hydrochloric acid for 0.75 h. The cooled reaction mixture was diluted with H_2O (20 ml), neutralized with sodium bicarbonate to pH 7, extracted with chloroform, dried (Na_2SO_4), and evaporated to leave crude **18**, 144 mg (84%), $[\alpha]^{28}D$ +20.2° (c 4.35, $CHCl_3$). The ir and NMR spectra were superimposable upon the spectra of **1E** obtained via path B.

Tetrasubstituted **18** gave a yellow crystalline picrate as needles from ethanol, mp 109.5–110.5 °C. An admixture with the picrate derived via **16** melted at 109–109.8 °C.

An analytical sample was prepared by repeated recrystallization from ethanol, mp 109.5–109.8 °C.

Anal. Calcd for $C_{16}H_{21}N_5O_7$: C, 48.6; H, 5.35; N, 17.7. Found: C, 48.3; H, 5.47; N, 17.6.

NMR Kinetics. An approximate assessment of the rate of the thermal rearrangement was determined in pyridine d_5 on **3b** at 89 °C. The extent of rearrangement was determined by integration of the C-5 methyl group.

3b (38 mg) in pyridine-d_5 (450 μl) was heated at 89 °C in the probe of a 90-MHz spectrometer. After 60 min integration showed 87% rearrangement to the pyrazolin-4-one **4b**.

3b (37 mg) in pyridine-d_5 (450 μl) containing CF_3CO_2H (5 μl) was heated at the same temperature as before. After 26 min integration showed 50% rearrangement and after 65 min the compound appeared 91% rearranged to pyrazolin-4-one **4b**.

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Registry No.—**1a**, 54123-69-2; **1b**, 59434-24-1; **1c**, 59434-25-2; **1d**, 54123-68-1; **1e**, 59434-26-3; **2a**, 54123-79-4; **2b**, 59434-27-4; **2c**, 59434-28-5; **2d**, 54123-78-3; **2e**, 59434-29-6; **3a**, 59434-30-9; **3b**, 59434-31-0; **3c**, 59434-32-1; **3d**, 59434-33-2; **3e**, 59434-34-3; **4a**, 59434-35-4; **4b**, 59434-36-5; **4c**, 59434-37-6; **4d**, 59434-38-7; **9**, 59448-78-1; **12**, 67-51-6; **16**, 59434-39-8; **17**, 59434-40-1; **18**, 59434-41-2; **18** picrate, 59434-42-3; **19**, 59434-43-4; methyl valerate, 624-24-8; MVL, 42722-80-5; hydrazine hydrate, 10217-52-4; *dl*-methyl α-methylbutyrate, 53955-81-0; methyl pivalate, 598-98-1; methyl benzoate, 93-58-3; (+)-methyl α-methylbutyrate, 10307-60-5.

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