

oxo-1,2,3,4,6,7,8,8a-octahydro-2-naphthoate (6).—The procedure was identical with that described for the methoxymethyl enol ether 10a. Reaction of 5.00 g (20.0 mmol) of β -keto ester 6⁹ gave 5.60 g of the crude methoxymethyl enol ether as a yellow oil. This material was used in the lithium-ammonia reduction step without further purification. Glpc analysis (column A, 178°, 200 ml/min) of the crude product revealed a single peak. The infrared spectrum of the crude enol ether showed bands at 1710 (C=O) and 1610 (conjugated double bond) cm^{-1} .

Ethyl 8 α ,8 β -Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2 β -naphthoate (8) by Reduction of Methoxymethyl Enol Ether 7b.—The procedure was identical with that described for the reduction of the methoxymethyl enol ether 10a. Reduction of 5.60 g of the crude methoxymethyl enol ether 7b with 750 mg (0.108 g-atom) of lithium gave 4.76 g of a yellow oil which showed a single peak on glpc analysis (column A, 163°, 200 ml/min). Chromatography of the crude product on 80 g of Woelm neutral alumina (activity II) and elution with 10% ether in petroleum ether (bp 30–60°) gave 2.86 g (61% from β -keto ester 6) of ester 8 as a colorless oil. An analytical sample was obtained by preparative glpc (column B, 168°): n_D^{25} 1.4907; ir 1729 (C=O), 1193, and 1041 cm^{-1} ; nmr τ 4.68 (m, 1 H), 5.88 (quartet, 2 H, $J = 7.0$ Hz), 8.73 (t, 3 H, $J = 7.0$ Hz), 9.01 (s, 3 H), and 9.07 (d, 3 H, $J = \sim 7$ Hz).

Anal. Calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2$: C, 76.23; H, 10.24. Found: C, 76.09; H, 10.07.

Ester 8 by Reduction of the Methyl Enol Ether 7a.—The procedure was similar to that used in the reduction of methoxymethyl enol ether 10a. A solution of 350 mg (1.33 mmol) of the methyl enol ether 7a⁹ was added with stirring to a dark blue solution of 50 mg (0.0072 g-atom) of lithium in 22 ml of anhydrous ammonia under argon. The solution was stirred for 1.0 hr at the liquid ammonia boiling point and was then cooled in powdered Dry Ice before quenching with 2.0 g of ammonium chloride. After addition of 25 ml of ether, evaporation of the ammonia, filtration, and evaporation of the ether, 312 mg of a slightly yellow oil was

obtained. Glpc analysis (column A, 166°, 200 ml/min) revealed that there was essentially only one peak. Purification of the oil by preparative glpc (column B, 167°) gave 210 mg (67%) of ester 8 which was found to be identical with that obtained above.

Ethyl 8 α ,8 β -Dimethyl-1,2,3,4,6,7,8,8a-octahydro-2 α -naphthoate (9).—To a solution of sodium ethoxide prepared from 280 mg (0.012 g-atom) of sodium and 17 ml of absolute ethanol was added a solution of 200 mg (0.85 mmol) of ester 8 in 3 ml of ethanol. After refluxing for 1.25 hr under nitrogen, the solution was cooled and poured into ice-cold water, and the resulting basic aqueous solution was extracted with petroleum ether (bp 30–60°). The petroleum ether extract was washed with water, dried with sodium sulfate, and evaporated to give 202 mg of a yellow oil. Preparative glpc (column B, 162°) of the oil gave 65 mg (33%) of ester 9 as a colorless oil: ir 1730 cm^{-1} nmr τ 4.70 (m, 1 H), 5.96 (quartet, 2 H, $J = 7.0$ Hz), 8.79 (t, 3 H, $J = 7.0$ Hz), 8.88 (s, 3 H), and 9.07 (d, 3 H, $J = 6.5$ Hz). The glpc and nmr data showed that no ester 8 remained after equilibration.

Anal. Calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2$: C, 76.23; H, 10.24. Found: C, 76.02; H, 10.27.

Registry No.—(±)-Eremoligenol, 22343-25-5; (±)-eremophilene, 22343-24-4; (±)-valerianol, 24741-63-7; (±)-valencene, 24741-64-8; 7b, 24799-48-2; 8, 24744-07-8; 9, 24744-08-9; 10a, 24744-09-0; 10b, 24744-10-3; 11, 22343-27-7; 12, 24744-12-5.

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Reduction of β -Keto Ester Methoxymethyl Enol Ethers to Saturated Esters with Lithium in Liquid Ammonia¹

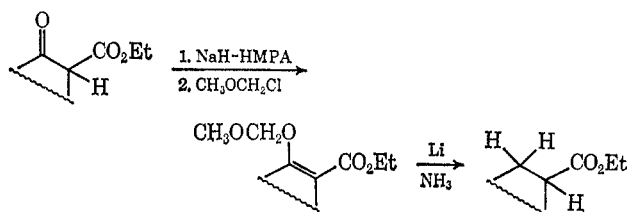
ROBERT M. COATES AND JAMES E. SHAW²

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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Methoxymethylation of a series of β -keto esters in hexamethylphosphoramide gave, with one exception, high proportions (96–100%) of O-alkylation. The reduction of the enol ethers with lithium in liquid ammonia furnished the corresponding saturated esters in variable overall yields (23–61%). This new method for reducing the ketone group of a β -keto ester is apparently most efficient with relatively hindered compounds.

We have recently described a new synthetic procedure for the reduction of a β -keto ester to a saturated ester.³ The method consists of first conversion to the methoxymethyl enol ether by alkylation of the sodium salt of the β -keto ester with chloromethyl methyl ether in hexamethylphosphoramide. The enol ether without purification is then subjected to reaction with lithium in liquid ammonia which effects a "double" reduction to the saturated ester.



(1) Taken in part from Ph.D. Thesis of J. E. S., University of Illinois, Urbana, 1969.

(2) National Science Foundation Trainee, 1965–1969.

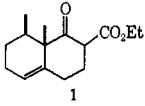
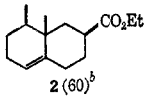
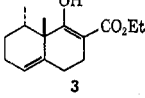
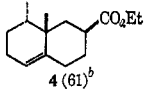
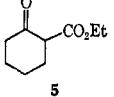
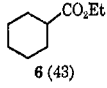
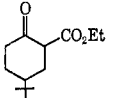
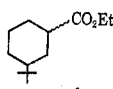
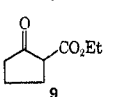
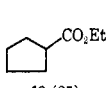
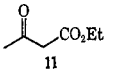
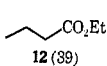
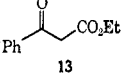
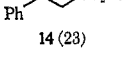
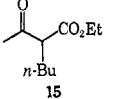
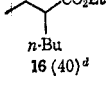
(3) R. M. Coates and J. E. Shaw, *J. Org. Chem.*, **35**, 2597 (1970); see also *Tetrahedron Lett.*, 5405 (1968).

In order to explore the generality of this method, we have applied the two-step sequence to a series of cyclic and acyclic β -keto esters. The results of this investigation are summarized in Table I.

In all cases except ethyl 2-*n*-butylacetoacetate (15), the reaction of the sodium enolate with chloromethyl methyl ether produced essentially exclusive O-alkylation. When less polar aprotic solvents were used instead of hexamethylphosphoramide, the amount of O-alkylated product decreased. In hexamethylphosphoramide the relative percentages of O- and C-alkylation for 2-carbethoxycyclohexanone (5) were 97 and 3%, respectively, but in 1,2-dimethoxyethane the corresponding values were 75 and 25%. In dimethyl sulfoxide there was 90% O-alkylation and 10% C-alkylation. The effect of the alkylating agent in promoting O-alkylation can be seen by comparison with results reported by other workers.⁴ Alkylation of the sodium enolate of ethyl acetoacetate (11) in hexa-

(4) A. L. Kurz, I. P. Beletskaya, A. Macías, and O. A. Reutov, *Tetrahedron Lett.*, 3679 (1968).

TABLE I
PREPARATION AND REDUCTION OF METHOXYMETHYL
ENOL ETHERS OF VARIOUS β -KETO ESTERS

β -Keto ester	Methoxymethyl enol ether, O/C ratio (yield, %)	Reduction product, (overall yield, ^a %)
	100/0 ^b	 2 (60) ^b
	100/0 ^b	 4 (61) ^b
	97/3 (82)	 6 (43)
	96/4 (79)	 8 (40) ^c
	97/3 (92)	 10 (25)
	100/0 (84)	 12 (39)
	98/2	 14 (23)
	69/31	 16 (40) ^d

^a From the β -keto ester. ^b For details see reference in footnote 3. ^c *trans* to *cis* isomer ratio, 70:30. ^d Yield in this case from the methoxymethyl enol ether.

methylphosphoramidate with ethyl chloride at room temperature has been reported to give 60 and 40% of the O- and C-alkylation products respectively. As shown in Table I, alkylation of ethyl acetoacetate with chloromethyl methyl ether gave only the O-alkylated product.⁵

The infrared spectra of the various methoxymethyl enol ethers show bands at approximately 1715 and 1635 cm^{-1} for the conjugated ester carbonyl and conjugated double bond, respectively. In the case of the acyclic enol ethers there is the possibility of *cis* and *trans* isomerism about the double bond. However, the nmr spectra indicate that only one isomer is present in each case. This isomer may be the *trans* if chelation to the sodium ion in the enolate anion is an important stabilizing factor. The nmr spectra of the methoxymethyl enol ethers of 2-carbomethoxycyclohexanone (5), 2-carbomethoxy-4-*t*-butylcyclohexanone (7), and 2-carbomethoxycyclopentanone (9) show the methylene group bonded to the two oxygen atoms as singlets at τ 5.13, 5.13, and 5.02, respectively. The enol ethers of ethyl acetoacetate (11), ethyl benzoylacetate (13), and ethyl 2-*n*-butylacetoacetate (15) show two-proton singlets at τ 5.02, 4.89, and 5.01, respectively. The similarity of these chemical shifts in both the cyclic and acyclic enol

ethers provides some support for a *trans* geometry in the acyclic enol ethers. In the nmr spectra of the C-alkylated isomers from 5 and 15, the methylene groups bonded to the methoxy groups appear as AB doublets at higher field centered at τ 6.44 ($J_{AB} = 9$ Hz, $\Delta\nu_{AB} = 13$ Hz) and τ 6.37 ($J_{AB} = 9.5$ Hz, $\Delta\nu_{AB} = 6.5$ Hz), respectively. The nonequivalence of the two geminal protons can be attributed to the asymmetric molecular environment.

Reduction of the methoxymethyl enol ethers of the various β -keto esters with excess lithium in liquid ammonia gave the products and yields shown in Table I. The ester products listed were essentially the only compounds found upon glpc analysis of the somewhat viscous crude products. Since the weights of the crude products corresponded to the theoretical amount, the remainder of the material must have been relatively nonvolatile substance. Dimeric or polymeric materials could be formed by coupling of anion radical intermediates or by acylation of anion radicals with other ester molecules.^{6,7} In the cases of the enol ethers of the bicyclic β -keto esters 1 and 3, steric hindrance might suppress such intermolecular reactions thus accounting for the higher yields of the reduced esters.

Lithium-ammonia reduction of ethyl cinnamate gave an 18% yield of ethyl hydrocinnamate (14). This is close to the 23% yield of ethyl hydrocinnamate obtained by lithium-ammonia reduction of the methoxymethyl enol ether of ethyl benzoylacetate (13) and indicated that the enol ether leaving group ($-\text{OCH}_2\text{OCH}_3$) was not responsible to any great extent for the low yield of ester product. However, lithium-ammonia reduction of *trans*-cinnamic acid gave a 65% yield of hydrocinnamic acid.⁸ This difference in yields could be due to elimination of intermolecular acylation in the reduction of the acid or alternatively the repression of coupling between the doubly charged dianion radical intermediates from cinnamic acid. When the methoxymethyl enol ether of 2-carbomethoxycyclohexanone was reduced in the presence of one equivalent of *t*-butyl alcohol in hopes of decreasing the amount of intermolecular side reactions, "overreduction" occurred to give primary alcohol in addition to the normal ester product. Apparently the *t*-butyl alcohol protonates the enolate anion of the ester, and then the ester can be further reduced with excess lithium to the primary alcohol. The combined yield of alcohol and ester was approximately the same as the yield of the ester in the absence of *t*-butyl alcohol. Primary alcohol was also produced if too much lithium was used in the reductions. The alcohol is probably formed when the reaction is quenched with ammonium chloride.⁹

In the reduction of the methoxymethyl enol ether of ethyl 2-carbomethoxy-4-*t*-butylcyclohexanone (7), glpc analysis of the crude product revealed that the relative percentages of *trans* and *cis* ethyl 3-*t*-butylcyclohexanecarboxylate (8) were 70 and 30%, respectively. Evi-

(6) Cf. R. G. Carlson and R. G. Blecke, *Chem. Commun.*, 93 (1969).

(7) The possibility that ester was being lost owing to reaction with ammonia after quenching with ammonium chloride was eliminated by the observation that ethyl cyclohexanecarboxylate could be completely recovered after it was added in ether to a solution of ammonia and ammonium chloride.

(8) This result suggests that prior hydrolysis of the enol ether ester to the acid then reduction might improve the yields. We have not had the opportunity to investigate this possibility.

(9) D. S. Watt, J. M. McKenna, and T. A. Spencer, *J. Org. Chem.*, **32**, 2674 (1967).

(5) See also J. L. Simonsen and R. Storey, *J. Chem. Soc.*, 2106 (1909).

dence that the major isomer had the carbethoxy group axial and *trans* to the equatorial *t*-butyl group was obtained by equilibration with sodium ethoxide in ethanol to a mixture consisting of 25% *trans* and 75% *cis* ethyl 3-*t*-butylcyclohexanecarboxylate. The predominance of the *trans* (axial) ester in the reduction product mixture indicates a significant preference for equatorial protonation even in the absence of an opposing axial substituent as in the bicyclic esters. This result contrasts with the absence of selectivity found in the protonation of the enolate anion of 4-*t*-butylacetylcyclohexane with acetic acid,¹⁰ but is comparable with the selectivity (60–65% equatorial protonation) observed in the ketonization of the enol of 4-phenylacetylcyclohexane with ammonium chloride as proton donor.¹¹

It should be pointed out that other enol derivatives of β -keto esters will undergo this reduction in lithium–ammonia solutions. The enol acetate of the bicyclic β -keto ester **1** was reduced to the same octalin ester (**2**) but in substantially lower yield (34% overall).³ The methyl enol ether of **3** was converted to ester **4** in 67% yield,³ an efficiency comparable to that obtained with the methoxymethyl analog. Since the preparation of methyl (or other alkyl) enol ethers is more likely to be complicated by C-alkylation,¹² the use of the methoxymethyl enol ether appears to be preferable.

The range in the overall yields (23 to 61%) of the saturated esters in the two-step sequence is evidently due mostly to the variations in the lithium–ammonia reduction step. Since the yields are best with the hindered β -keto esters, the method should provide a useful complement to existing chemical procedures.¹³ In addition the generation of the less stable ester epimer (*e.g.*, from **1** and **3**) may be of stereochemical advantage.

Experimental Section¹⁴

2-Carboethoxycyclohexanone Methoxymethyl Enol Ether.—To a cooled mixture of 1.32 g (33.0 mmol) of 60% dispersion of sodium hydride in mineral oil and 90 ml of dry hexamethylphosphoramide under nitrogen was added a solution of 5.10 g (30.0 mmol) of 2-carboethoxycyclohexanone (**5**) in 10 ml of hexamethylphosphoramide. The solution was stirred for 1.0 hr at room temperature. The solution was then cooled, and 2.90 g (36.0 mmol) of chloromethyl methyl ether was added with stirring. After 2.0 hr at room temperature the solution was cooled

(10) H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).

(11) H. E. Zimmerman and P. S. Mariano, *J. Amer. Chem. Soc.*, **90**, 6091 (1968).

(12) G. Brieger and W. M. Pelletier, *Tetrahedron Lett.*, 3555 (1965); W. J. le Noble and J. E. Puerta, *ibid.*, 1087 (1966); S. J. Rhoads and R. W. Hasbrouch, *Tetrahedron*, **22**, 3557 (1966); W. J. le Noble and H. F. Morris, *J. Org. Chem.*, **34**, 1969 (1964); A. L. Kurta, I. P. Beletskaya, A. Maofas, and S. S. Yafit, *J. Org. Chem. USSR*, **4**, 1327 (1968); S. J. Rhoads and R. W. Holder, *Tetrahedron*, **25**, 5443 (1969).

(13) (a) Clemmenson reduction: A. Afonso, *J. Amer. Chem. Soc.*, **90**, 7375 (1968). (b) Thioketal desulfurization: G. Stork and J. W. Schulenberg, *ibid.*, **84**, 284 (1962); T. A. Spencer, T. D. Weaver, R. M. Villalica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968); K. Mori and M. Matsui, *Tetrahedron*, **24**, 3095 (1968).

(14) Infrared spectra were recorded with a Perkin-Elmer Model 137 or Model 521 spectrometer. Carbon tetrachloride solutions were used unless otherwise specified and were calibrated with the polystyrene band at 1603 cm^{-1} . Nmr spectra were determined in carbon tetrachloride solution with a Varian Associates Model A-60A or A-56-60 spectrometer using tetramethylsilane as an internal standard. Microanalyses were determined in the University of Illinois microanalytical laboratory. Gas chromatography (glpc) was performed on a Wilkens Aerograph A-90-P instrument employing helium as the carrier gas. The following columns were used: a 5 ft \times 0.25 in. column of 20% SE-30 on 60–80 mesh Chromosorb W (column A), a 6 ft \times 1/8 in. column of 20% SE-30 on 60–80 mesh Chromosorb W (column B), a 5 ft \times 0.25 in. column of 3% SE-30 on 60–80 mesh Chromosorb W (column C).

and poured into 50 ml of ice-cold saturated sodium bicarbonate solution. The sodium bicarbonate solution was diluted with 50 ml of water and was then extracted with two 100 ml-ports of ether. The ether solution was washed three times with 40–50-ml portions of water, dried with sodium sulfate, and evaporated under reduced pressure to give a yellow liquid. The liquid was mixed with 25 ml of petroleum ether (bp 30–60°) and was dried a second time with sodium sulfate. Evaporation under reduced pressure gave 6.60 g of the crude methoxymethyl enol ether as a yellow liquid which was used for the lithium–ammonia reduction step without further purification. Glpc analysis (column B, 145°, 200 ml/min) of the crude product revealed that it consisted of 97% of the methoxymethyl enol ether and 3% of the C-alkylated isomer and that the actual yield of the enol ether was 82%. An analytical sample of the C-alkylated isomer which had the shorter retention time was obtained by preparative glpc (column B, 137°). The infrared spectrum shows bands at 1715 (C=O) and 1740 (C=O) cm^{-1} . The nmr spectrum has absorptions at τ 5.84 (quartet, 2 H, $J = 7.0$ Hz), 6.72 (s, 3 H), and 8.74 (t, 3 H, $J = 7.0$ Hz). The methylene group bonded to the methoxy group appears as an AB system centered at τ 6.44 ($J_{AB} = 9.0$ Hz, $\Delta\nu_{AB} = 13$ Hz).

Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_4$: C, 61.66; H, 8.47. Found: C, 61.57; H, 8.25.

An analytical sample of the methoxymethyl enol ether was also obtained by preparative glpc (column B, 137°): n_D^{20} 1.4777; ir 1715 (C=O) and 1635 (conjugated C=C) cm^{-1} ; nmr τ 5.13 (s, 2 H), 5.92 (quartet, 2 H, $J = 7.0$ Hz), 6.61 (s, 3 H), and 8.75 (t, 3 H, $J = 7.0$ Hz).

Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_4$: C, 61.66; H, 8.47. Found: C, 61.75; H, 8.33.

When the above reaction was performed in the same manner except that 1,2-dimethoxyethane or dimethyl sulfoxide was used as the solvent instead of hexamethylphosphoramide, the amount of C-alkylation increased. In 1,2-dimethoxyethane there was 25% C-alkylation and 75% O-alkylation. In dimethyl sulfoxide there was 10% C-alkylation and 90% O-alkylation.

Reduction of 2-Carboethoxycyclohexanone Methoxymethyl Enol Ether.—A solution of 1.10 g of the crude methoxymethyl enol ether in 26 ml of ether was rapidly added to a magnetically stirred, dark blue solution of 250 mg (0.036 g-atom) of lithium in 82 ml of anhydrous ammonia under argon. Powdered Dry Ice was used to cool the reaction flask while this addition was made. After stirring for 12 min at the liquid ammonia boiling point (–33°), the solution was cooled for 6 min with powdered Dry Ice, and then 7.5 g of ammonium chloride was added essentially all at once to quench. The blue color of the solution actually faded 2 min before quenching. After 60 ml of ether was added, the Dry Ice–isopropyl alcohol condenser was replaced with a sodium hydroxide drying tube. The mixture was allowed to stand at room temperature until the ammonia had evaporated. The mixture was then filtered, and the inorganic salts were crushed and washed three times with ether. The ether solution was then evaporated to give 940 mg of a slightly yellow liquid. Glpc analysis (column B, 100°, 150 ml/min) of this liquid revealed that there was essentially only one volatile compound. This compound was collected by preparative glpc (column B, 105°) and was found to be identical to ethyl cyclohexanecarboxylate (**6**) by comparison of infrared and nmr spectra and glpc retention times. The actual yield of ethyl cyclohexanecarboxylate was determined to be 321 mg (41% from β -keto ester **5**) by glpc (column B, 107°, 200 ml/min) using ethyl phenylacetate as an internal standard. A second reduction of the crude enol ether under the same conditions gave a 46% overall yield of **6**.

2-Carboethoxycyclopentanone Methoxymethyl Enol Ether.—Reaction¹⁵ of 4.68 g (30.0 mmol) of 2-carboethoxycyclopentanone (**9**) gave 6.20 g of the crude methoxymethyl enol ether as a yellow liquid. This material was used for the lithium–ammonia reduction step without further purification. Glpc analysis (column A, 140°, 150 ml/min) of the crude product revealed that it consisted of 97% of the methoxymethyl enol ether and 3% of the C-alkylated isomer and that the actual yield of the enol ether was 92%. The C-alkylated isomer which had the shorter retention time was obtained as a colorless liquid by preparative glpc (column B, 133°) and was characterized only by its infrared spectrum which shows bands at 1755 (C=O) and 1730 (C=O)

(15) The detailed procedure described for the preparation (or reduction) of the methoxymethyl enol ether of 2-carboethoxycyclohexanone was followed.

cm^{-1} . An analytical sample of the methoxymethyl enol ether was obtained by preparative glpc (column B, 133°): n_D^{20} 1.4767; ir (film) bands at 1715 (C=O) and 1635 (conjugated C=C) cm^{-1} ; nmr τ 5.02 (s, 2 H), 5.92 (quartet, 2 H, $J = 7.0$ Hz), 6.57 (s, 3 H), and 8.76 (t, 3 H, $J = 7.0$ Hz).

Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_4$: C, 59.98; H, 8.05. Found: C, 60.08; H, 7.98.

Reduction of 2-Carboethoxycyclopentanone Methoxymethyl Enol Ether.—Reduction¹⁵ of 1.02 g of the crude methoxymethyl enol ether with 250 mg (0.036 g-atom) of lithium gave 766 mg of a slightly yellow liquid which contained essentially only one volatile compound on glpc analysis (column B, 93°, 200 ml/min). This material was collected by preparative glpc (column B, 93°) and was shown to be identical to ethyl cyclopentanecarboxylate (10) by comparison of infrared spectra and glpc retention times. The actual yield of 10 was determined to be 177 mg (25%) from 9 by glpc (column B, 93°, 200 ml/min) using ethyl cyclohexanecarboxylate as an internal standard. A second reduction of the crude enol ether by the same procedure except that 210 mg of lithium was used gave a 11% overall yield of 10. When 275 mg of lithium was used, some ethyl cyclopentanecarboxylate was reduced to the primary alcohol, and the combined overall yield of ester and alcohol was 24%.

2-Carboethoxy-4-*t*-butylcyclohexanone Methoxymethyl Enol Ether.—Reaction¹⁵ of 6.78 g (30.0 mmol) of 2-carboethoxy-4-*t*-butylcyclohexanone (7) gave 8.35 g of the crude methoxymethyl enol ether as a yellow liquid. This material was used for the lithium-ammonia reduction step without further purification. Glpc analysis (column B, 183°, 200 ml/min) of the crude product revealed that it consisted of 96% of the methoxymethyl enol ether and 4% of the C-alkylated isomer and that the actual yield of the enol ether was 79%. The C-alkylated isomer which had the shorter retention time was obtained as a colorless liquid by preparative glpc (column B, 183°) and was characterized only by its infrared spectrum which shows bands at 1730 (C=O) and 1705 (C=O) cm^{-1} . An analytical sample of the methoxymethyl enol ether was obtained by preparative glpc (column B, 183°): n_D^{20} 1.4772; ir (film) 1715 (C=O) and 1635 (conjugated C=C) cm^{-1} ; nmr τ 5.13 (s, 2 H), 5.90 (quartet, 2 H, $J = 7.0$ Hz), 6.60 (s, 3 H), 8.74 (t, 3 H, $J = 7.0$ Hz), and 9.07 (s, 9 H).

Anal. Calcd for $\text{C}_{15}\text{H}_{26}\text{O}_4$: C, 66.64; H, 9.69. Found: C, 66.66; H, 9.84.

Reduction of 2-Carboethoxy-4-*t*-butylcyclohexanone Methoxymethyl Enol Ether.—Reduction¹⁵ of 1.38 g of the crude methoxymethyl enol ether with 240 mg (0.035 g-atom) of lithium gave 1.23 g of a slightly yellow liquid. Glpc analysis (column A, 138°, 200 ml/min) revealed that it consisted of 30% ethyl *cis*-3-*t*-butylcyclohexanecarboxylate (*cis*-8) and 70% ethyl *trans*-3-*t*-butylcyclohexanecarboxylate (*trans*-8). An analytical sample of the *trans* isomer which had the shorter retention time was obtained by preparative glpc (column B, 133°): n_D^{20} 1.4522; ir (film) 1735 (C=O), 1200, 1180, 1160, 1145, and 1035 cm^{-1} ; nmr τ 5.91 (quartet, 2 H, $J = 7.0$ Hz), 8.76 (t, 3 H, $J = 7.0$ Hz), and 9.14 (s, 9 H).

Anal. Calcd for $\text{C}_{13}\text{H}_{24}\text{O}_2$: C, 73.54; H, 11.39. Found: C, 73.24; H, 11.22.

An analytical sample of the *cis* isomer was also obtained by preparative glpc: n_D^{20} 1.4535; ir (film) bands at 1735 (C=O), 1190, 1155, and 1040 cm^{-1} ; nmr τ 5.95 (quartet, 2 H, $J = 7.0$ Hz), 8.77 (t, 3 H, $J = 7.0$ Hz), and 9.11 (s, 9 H).

Anal. Calcd for $\text{C}_{13}\text{H}_{24}\text{O}_2$: C, 73.54; H, 11.39. Found: C, 73.88; H, 11.42.

The combined actual yield of the *cis* and *trans* esters was determined to be 424 mg (40% from 7) by glpc (column B, 133°, 200 ml/min) using diethyl phthalate as an internal standard. When 200 mg (0.94 mmol) of the 70:30 mixture of *trans* and *cis* esters was refluxed for 35 min with a solution of sodium ethoxide prepared from 300 mg (0.013 g-atom) of sodium and 20 ml of absolute ethanol, the relative amounts of the *cis* and *trans* esters changed to 75 and 25%, respectively. Further heating at reflux did not change these percentages.

Ethyl Benzoylacetate Methoxymethyl Enol Ether.—Reaction¹⁵ of 5.76 g (30.0 mmol) of ethyl benzoylacetate 13 gave 7.24 g of the crude methoxymethyl enol ether as a yellow liquid. This material was used for the lithium-ammonia reduction step without further purification. Glpc analysis (column C, 160°, 150 ml/min) of the crude product revealed that it consisted of 98% the methoxymethyl enol ether and 2% an unidentified compound which was probably the C-alkylated isomer. Purification of the enol ether by preparative glpc (column A, 168°) was not

possible owing to decomposition under the glpc conditions. The infrared spectrum (film) of the crude product shows bands at 1715 (C=O) and 1625 (conjugated C=C) cm^{-1} . The nmr spectrum shows absorptions at τ 4.40 (s, 1 H), 4.89 (s, 2 H), 5.89 (quartet, 2 H, $J = 7.0$ Hz), 6.49 (s, 3 H), and 8.73 (t, 3 H, $J = 7.0$ Hz).

Reduction of Ethyl Benzoylacetate Methoxymethyl Enol Ether.—Reduction¹⁵ of 1.21 g of the crude methoxymethyl enol ether with 250 mg (0.036 g-atom) of lithium gave 958 mg of a viscous yellow liquid which contained only one volatile component on glpc analysis (column B, 121°, 150 ml/min). This material was collected by preparative glpc (column B, 129°) and was shown to be identical to ethyl hydrocinnamate (14) by comparison of infrared and nmr spectra. The actual yield of 14 was determined to be 196 mg (22% from 13) by glpc (column B, 121°, 150 ml/min) using ethyl phenylacetate as an internal standard. A second reduction of the crude enol ether by the same procedure, except that 210 mg of lithium was used, gave a 23% overall yield of ethyl hydrocinnamate. When 190 mg of lithium was used, the overall yield was 19%.

Ethyl 2-*n*-Butylacetoacetate Methoxymethyl Enol Ether.—Reaction¹⁵ of 5.58 g (30.0 mmol) of ethyl 2-*n*-butylacetoacetate (15) gave 7.21 g of a yellow liquid. Glpc analysis (column A, 140°, 200 ml/min) of the crude product revealed that it consisted of 69% the methoxymethyl enol ether and 31% the C-alkylated isomer. An analytical sample of the C-alkylated isomer which had the shorter retention time was obtained by preparative glpc (column B, 152°): ir (film) 1740 (C=O) and 1715 (C=O) cm^{-1} ; τ 5.85 (quartet, 2 H, $J = 7.0$ Hz), AB system centered at 6.37 (–OCH₂O–, $J_{AB} = 9.5$ Hz, $\Delta\nu_{AB} = 6.5$ Hz), 6.70 (s, 3 H), 7.92 (s, 3 H), 8.73 (t, 3 H, $J = 7.0$ Hz), and 9.08 (t, 3 H, $J = \sim 6$ Hz).

Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{O}_4$: C, 62.58; H, 9.63. Found: C, 62.90; H, 9.57.

An analytical sample of the methoxymethyl enol ether was also obtained by preparative glpc: n_D^{20} 1.4567; ir (film) 1710 (C=O) and 1630 (conjugated C=C) cm^{-1} ; nmr τ 5.01 (s, 2 H), 5.90 (quartet, 2 H, $J = 7.0$ Hz), 6.59 (s, 3 H), 7.68 (s, 3 H), 8.73 (t, 3 H, $J = 7.0$ Hz), and 9.09 (t, 3 H, $J = \sim 6$ Hz).

Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{O}_4$: C, 62.58; H, 9.63. Found: C, 62.75; H, 9.65.

An attempt to purify the enol ether by distillation using a Vigreux column was only partially successful. Column chromatography on Woelm neutral alumina (activity II) and elution with 0–2% ether in petroleum ether (bp 30–60°) gave the pure methoxymethyl enol ether.

Reduction of Ethyl 2-*n*-Butylacetoacetate Methoxymethyl Enol Ether.—Reduction¹⁵ of 1.15 g (5.00 mmol) of the purified methoxymethyl enol ether with 250 mg (0.036 g-atom) of lithium gave 862 mg of a yellow liquid which contained essentially only one volatile compound as shown by glpc analysis (column B, 112°, 120 ml/min). This compound was collected by preparative glpc (column B, 108°) and found to be identical with ethyl 2-ethylhexanoate (16) by comparison of infrared and nmr spectra. The actual yield of (16) was determined by glpc (column B, 112°, 120 ml/min) to be 40% based on the enol ether. When the methoxymethyl enol ether was reduced with 275 mg of lithium by the same procedure, some ethyl 2-ethylhexanoate was reduced to the primary alcohol, and the combined yield of ester and alcohol was 43%.

Ethyl Acetoacetate Methoxymethyl Enol Ether.—Reaction¹⁵ of 3.90 g (30.0 mmol) of ethyl acetoacetate (11) gave 5.34 g of the crude methoxymethyl enol ether as a yellow liquid. This material was used for the lithium-ammonia reduction step without further purification. Glpc analysis (column B, 114°, 120 ml/min) of the liquid revealed that it consisted of only the methoxymethyl enol ether and that the yield of the enol ether was 84%. An analytical sample of this material was obtained by preparative glpc (column B, 114°): n_D^{20} 1.4522; ir (film) 1715 (C=O) and 1630 (conjugated C=C) cm^{-1} ; nmr τ 4.85 (s, 1 H), 5.02 (s, 2 H), 5.94 (quartet, 2 H, $J = 7.0$ Hz), 6.58 (s, 3 H), 7.72 (s, 3 H), and 8.76 (t, 3 H, $J = 7.0$ Hz).

Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_4$: C, 55.16; H, 8.10. Found: C, 55.20; H, 8.07.

Reduction of Ethyl Acetoacetate Methoxymethyl Enol Ether.—The procedure was exactly the same as that described for the reduction of 2-carboethoxycyclohexanone methoxymethyl enol ether except the ether solution was not evaporated in the work-up procedure. The crude methoxymethyl enol ether (890 mg) was reduced with 250 mg (0.036 g-atom) of lithium. After filtration

to remove the inorganic salts the ether solution was analyzed by glpc (column C, 64°, 120 ml/min) was found to contain essentially only one volatile compound. This compound was later collected by preparative glpc (column B, 73°) and was shown to be identical to ethyl butyrate by comparison of glpc retention times and infrared spectra. The actual yield of ethyl butyrate (12) in the ether solution was determined to be 225 mg (39% from 11) by glpc (column C, 64°, 120 ml/min) using mesitylene as an internal standard. A second yield determination was made by glpc on the residual liquid (1.20 g) remaining after the ether was distilled off through a Vigreux column at atmospheric pressure. The overall yield was found to be 35%.

Reduction of Ethyl Cinnamate.—Reduction¹⁵ of 880 mg (5.00 mmol) of ethyl cinnamate with 114 mg (0.016 g-atom) of lithium gave 983 mg of a viscous yellow liquid which contained only one volatile compound as shown by glpc (column B, 121°, 150 ml/min). This compound was found to be identical with ethyl hydrocinnamate (14) by comparison of infrared and nmr spectra. The actual yield of the ester was determined to be 18% by glpc (column B, 121°, 150 ml/min) using ethyl phenylacetate as an internal standard. A second reduction by the same procedure except that 128 mg of lithium was used gave a 16% yield of ethyl hydrocinnamate.

Reduction of *trans*-Cinnamic Acid.—A solution of 740 mg (5.0 mmol) of *trans*-cinnamic acid in 26 ml of ether was added with stirring to a solution of 148 mg (0.021 g-atom) of lithium in 82 ml of anhydrous ammonia under argon. The solution was stirred for 15 min at the liquid ammonia boiling point and was then cooled 5 min with powdered Dry Ice before quenching with 7.5 g of ammonium chloride. After addition of 60 ml of ether and evaporation of the ammonia, the reaction mixture was

acidified with 10% concentrated hydrochloric acid. The ether extract was washed with water, dried with sodium sulfate, and evaporated to give 743 mg of a viscous oil. Glpc analysis (column C, 142°, 120 ml/min) of the oil revealed that only hydrocinnamic acid was present and that the actual yield of the acid was 65%. Crystallization of the oil in petroleum ether (bp 30–60°) and recrystallization from the same solvent gave 390 mg (52%) of hydrocinnamic acid, mp 46–48° (lit.¹⁶ mp 48°). The infrared spectrum was identical with that of authentic hydrocinnamic acid.

Registry No.—2-Carboethoxycyclohexanone methoxymethyl enol ether, 25096-42-8; 2-carboethoxycyclopentanone methoxymethyl enol ether, 25096-43-9; 2-carboethoxy-4-*t*-butylcyclohexanone methoxymethyl enol ether, 25096-44-0; ethyl benzoylacetate methoxymethyl enol ether, 25096-45-1; ethyl 2-*n*-butylacetoacetate methoxymethyl enol ether, 25095-46-2; ethyl acetoacetate methoxymethyl enol ether, 25096-47-3; *cis*-8, 25096-48-4; *trans*-8, 25096-49-5.

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(16) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N.Y., 1964, p 312.

Isolation and Structure of Two New Germacranolides¹ from *Polymnia uedalia* (L.) L.

WERNER HERZ AND S. V. BHAT

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

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Examination of several collections of *Polymnia uedalia* (L.) L. yielded varying quantities of two new highly oxygenated germacranolides uvedalin (1a) and polydalin (1d) which were correlated. Experiments and spectroscopic studies which led to the determination of their structure are described. *P. laevigata* Beadle gave the eudesmanolide ivalin. The flavone artemetin was isolated from *P. canadensis* L., which contained only small amounts of sesquiterpene lactones.

As part of our general study of subtribe *Melampodiinae*, tribe *Heliantheae*, family *Compositae*,² we have investigated North American representatives of the genus *Polymnia* which is endemic to the Western Hemisphere.³ The isolation and structure determination of two new highly oxygenated germacranolides from *Polymnia uedalia* (L.) L. is reported herewith.

Collections of *P. uedalia* from Rabun County, Ga., Leon County, Fla., and W. Va. furnished two crystalline sesquiterpene lactones whose relative yield varied somewhat with location⁴ and which were named uvedalin and polydalin.

(1) Supported in part by grants from the National Science Foundation (GB-6413) and the U. S. Public Health Service (RG-05814).

(2) The original impetus for these studies is given by W. Herz, S. V. Bhat, and A. L. Hall, *J. Org. Chem.*, **35**, 1110 (1970).

(3) The most recent review of this genus is by J. R. Wells, *Brittonia*, **17**, 144 (1965).

(4) Although the three previously described^{5,6} varieties of *P. uedalia* are no longer recognized,⁸ the variation in lactone content might be due to the existence of separate chemical races. Material from both West Virginia and Georgia would have keyed out as var. *uedalia* although differing consistently in lactone content, while material from Florida, which chemically resembled the collection from Georgia, would have been assigned to var. *floridana*.⁹ This problem is receiving further attention from Dr. J. R. Wells.

(5) S. F. Blake, *Rhodora*, **19**, 46 (1917).

(6) J. R. Wells, *ibid.*, **71**, 786 (1969). We are indebted to Dr. Wells for authenticating the collections and for valuable correspondence.

Uvedalin (1a), C₂₃H₂₈O₉, mp 131–3°, [α]_D +12.8°, was a conjugated γ -lactone (ir bands at 1765 and 1665 cm⁻¹, with strong uv end absorption). The nmr spectrum (Table I) exhibited the typical two doublets (H_a and H_b) of partial structure A whose presence was confirmed by facile formation of a pyrazoline (2a) and by controlled sodium borohydride reduction to a dihydro derivative 3a in whose nmr spectrum the signals of H_a and H_b were replaced by a new methyl doublet. Spin-decoupling experiments involving H_a and H_b established the location of the H_c multiplet at 2.8 ppm; this in turn was coupled to two doublets of doublets at 5.00 and 6.55 ppm, one of which represented the H_d resonance.

The other doublet of doublets was tentatively assigned to hydrogen (H_e) under one of three ester functions whose presence was indicated by the consump-

