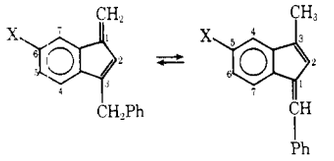
is added to clarify nomenclature. Indene is numbered beginning with the saturated carbon, C-1, of the five-membered ring. A prototropic shift must result in a new saturated carbon and, therefore, in reversal of the direction of numbering of the entire carbon skeleton. For example, a 6-subsituted



3-benzyl-1-methylideneindene upon isomerization of both double bonds becomes a 5-substituted 1-benzylidene-3-methylindene.

(3) Generic name for 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid; a potent, widely used antiinflammatory agent.
(4) T. Y. Shen, R. L. Ellis, B. E. Witzel, and A. R. Matzuk, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N.Y., Sept 1966, No. P003.
(5) K. Hoogsteen and N. R. Trenner, *J. Org. Chem.*, **35**, 521 (1970).
(6) S. H. Pines and A. W. Douglas, *J. Am. Chem. Soc.*, **98**, 8119 (1976).
(7) R. E. Merrill and E. Negishi, *J. Org. Chem.*, **39**, 3452 (1974).
(8) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *J. Org. Chem.*, **23**, 1832 (1958).
(9) M. Selim, H. Gault, and J. Delahaye, *C. R. Acad. Sci.*, **257**, 4191 (1963); *Chem. Abstr.*, **60**, 5328*f* (1964).
(10) A. Markovac, M. P. LaMontagne, P. Blumbergs, A. B. Ash, and C. L. Stevens, *J. Med. Chem.*, **15**, 918 (1972).
(11) J. Schreiber, C.-G. Wermuth, and A. Meyer, *Bull. Soc. Chim. Fr.*, 625 (1973).
(12) (a) Y. Sprinzak, *J. Am. Chem. Soc.*, **80**, 5449 (1958); (b) M. Avramoff and Y. Sprinzak, *Ibid.*, **82**, 4945 (1960).
(13) (a) C. Weizmann, U.S. Patent 2 592 365 (1952); (b) A. M. Weidler, *Acta Chem. Scand.*, **17**, 2724 (1963); *Chem. Abstr.*, **60**, 1049*c* (1964); (c) G. Bergson, *Acta Chem. Scand.*, **17**, 2691 (1963); *Chem. Abstr.*, **60**, 10494*b* (1964); (d) M. Makosza, Polish Patent 55,535 (1968); *Chem. Abstr.*, **70**, 106254w (1969); (e) M. Neuenschwander, H. P. Fahrni, H. Lehmann, and R. Voegeli, *Chimia*, **28**, 115 (1974); *Chem. Abstr.*, **80**, 133106n (1974).
(14) (a) E. C. Friedrich and D. B. Taggart, *J. Org. Chem.*, **40**, 720 (1975). (b) L. Meurling, *Acta Chem. Scand.*, **28**, 399 (1974).
(15). E. Ghera and Y. Sprinzak, *J. Am. Chem. Soc.*, **82**, 4945 (1960).
(16) E. Haruki, M. Arakawa, N. Matsumura, Y. Otsuji, and E. Imoto, *Chem. Lett.*, 427–428 (1974); *Chem Abstr.*, **81**, 13305a (1974).
(17) E. Pfeil, *Chem. Ber.*, **84**, 229 (1951).
(18) L. Fieser and M. Fieser in "Advanced Organic Chemistry", Reinhold, New York, N.Y., 1961, pp 431–432.
(19) G. W. Gokel, H. M. Gerdes, and N. W. Rebert, *Tetrahedron Lett.*, 653 (1976).
(20) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
(21) S. H. Pines, R. F. Czaja, and N. L. Abramson, *J. Org. Chem.*, **40**, 1920 (1975).

The Regioselective Behavior of Unsaturated Keto Esters toward Vinylogous Amides

Gregory B. Bennett* and Robert B. Mason

Department of Medicinal Chemistry, Pharmaceutical Division, Sandoz, Inc., East Hanover, New Jersey 07936

Received October 19, 1976

The regioselective reactivity of unsaturated keto ester **8** toward vinylogous amides **7** and **11** is presented, along with further evidence as to the effect of solvent on the course of the reaction.

The regioselective synthesis of indoles or quinolines from the coupling of diacyl ethylenes (**2**) and primary enamino ketones (**1**) has been reported.[1] Under acidic or neutral reaction conditions the indole derivatives (**4**) are formed whereas basic and/or dehydrogenation conditions provide the corresponding quinolines (**6**) (Scheme I). Use of an unsymmetrical

Scheme I

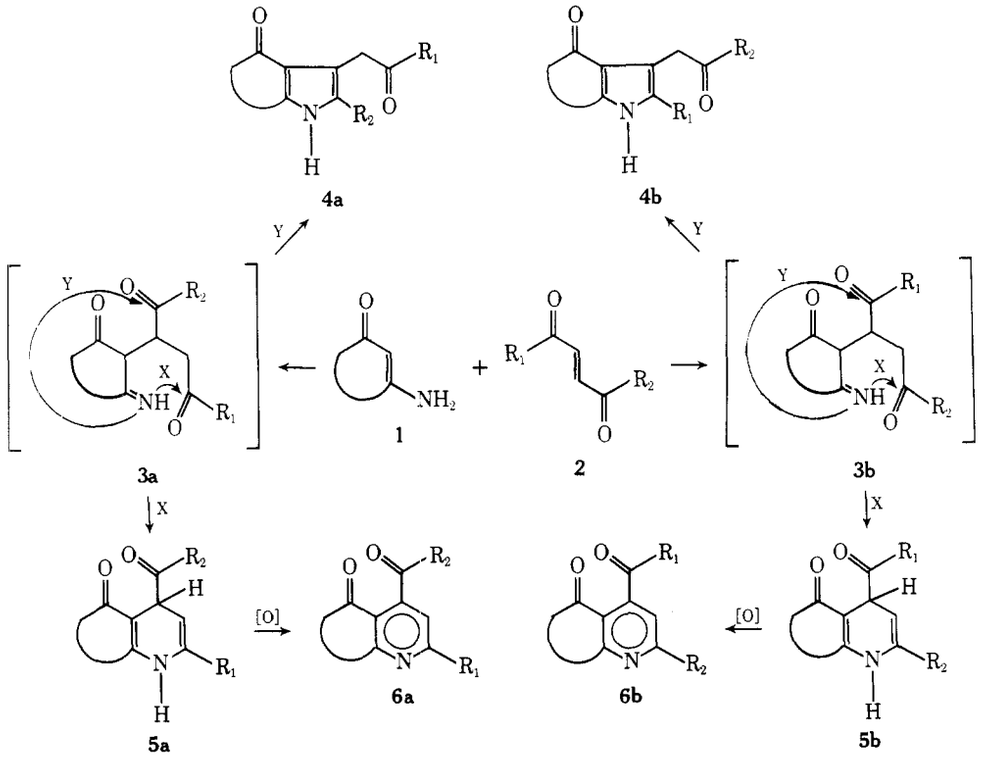


Table I. Calculated and Observed ^{13}C Absorptions Resonances[a]

	10a	10a calcd[c]	10c calcd[c]	10b
N_1CH_3[b]	28.4	28	28	28.1
C_2	150.7	150	150	150.4
N_3CH_3[b]	29.6	29	29	29.1
C_4	151.7	152	152	151.9
C_{4a}	104.5	107	111	108.3
C_5	144.7	140	156	138.0
C_6	112.7	114	107	114.7
C_7	160.5	162	152	161.5
C_{8a}	176.0	176	176	175.6
t-Bu-C	38.9	39	39	38.6
t-Bu-CH_3	29.8	30	30	30.0
CO_2CH_3	168.5	167	167	
CO_2CH_3	53.3	52	52	

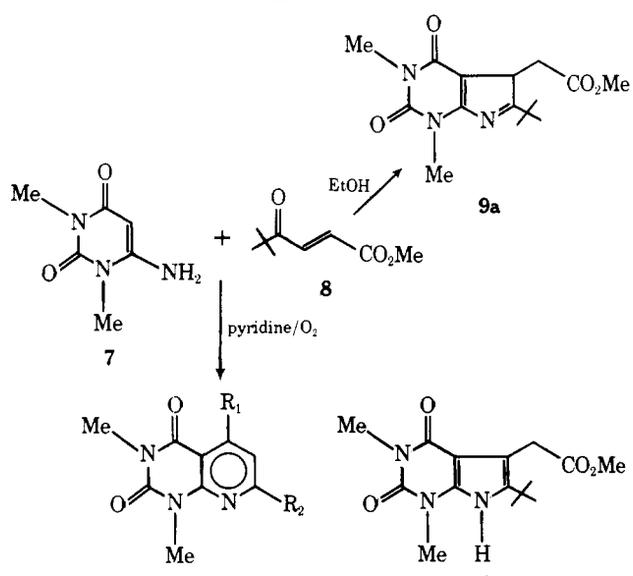
[a] Chemical shifts are reported in δ units using Me_4Si as the internal standard. [b] No distinction can be made between the absorption of N_1CH_3 and N_3CH_3. [c] The calculations were based on model compounds found in L. T. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra, A Collection of Assigned, Coded and Indexed Spectra", Wiley-Interscience, New York, N.Y., 1972.

unsaturated dicarbonyl compound (**2**, $R_1 \neq R_2$) could provide four products, **4a**, **4b**, **6a**, and **6b**. Conjugate addition 1,4 to COR_2 would lead through an intermediate such as **3b** to either **4b** or **6b** depending on the requirements for ring closure.[1] Likewise, addition 1,4 to COR_1 would provide intermediate **3a** and eventually product **4a** or **6a**.[2]

The potential for a directed process exists at two points along the reaction pathway: (1) during conjugate addition of **1** to **2** and (2) during ring closure. In the case where R_1 and R_2 are quite similar one would expect[1] a mixture of **4a** and **4b** or **6a** and **6b** depending on the reaction conditions. Based in part on the behavior of unsaturated keto esters toward such 1,3-dipolar species as diazomethane,[3] where R_1 and R_2 are dissimilar electronically, one would expect only one of the two possible isomers for each set of reaction conditions. Such is the case we wish to report.

Reaction of methyl 3-pivaloylacrylate (**8**)[4,5] and 6-amino-1,3-dimethyluracil (**7**) in refluxing pyridine provided quinoline

Scheme II



10a, $R_1 = CO_2Me$; $R_2 = t$-Bu
b, $R_1 = H$; $R_2 = t$-Bu
c, $R_1 = t$-Bu; $R_2 = CO_2Me$

10a as the only isolated product, in 36% yield. Initial nucleophilic attack on the unsaturated keto ester occurs 1,4 to the ketone. This is followed by ring closure to the ketone and not to the ester.

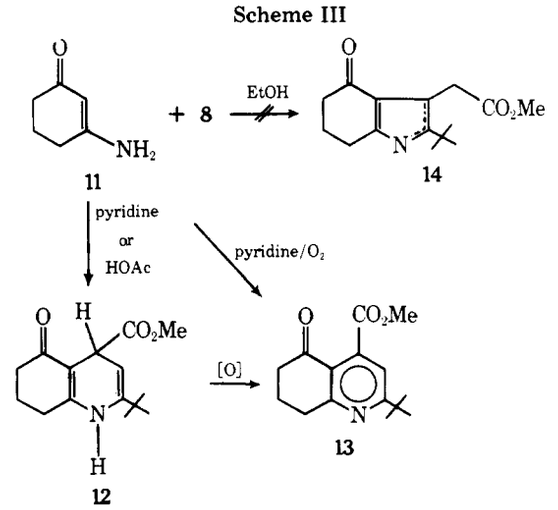
A comparison of the ^{13}C NMR spectrum of **10a** with the calculated ^{13}C NMR spectra for **10a** and **10c** helped confirm the structural assignment (see Table I). Compound **10b**, whose structure had been determined by ^{13}C NMR spectroscopy,[6] was used as the model system for these calculations.

When the same starting materials, **7** and **8**, were heated in refluxing EtOH, tetrahydroindole **9a** was isolated in only 14% yield. Once again, no other products resulting from a one-to-one combination of substrates could be observed.[7] Initial nucleophilic attack has taken place 1,4 to the ester, with subsequent ring closure to the ketone and not to the ester. That the product is isolated in the indolenine and not the indole (**9b**) tautomeric form is somewhat surprising. One rationalization for this observation would be that the indolenine form (**9a**) allows for more relief of the steric interaction between the *tert*-butyl and acetate moieties than the aromatic indole tautomer (**9b**). The assignment of structure was based on an evaluation of the product's 100-MHz ^1H NMR spectrum.

The regiospecific behavior displayed by unsaturated keto ester **8** toward vinylogous amide **7** during Michael addition is influenced by reaction conditions, whereas cyclization between imine and ketone is preferred in all cases to cyclization between imine and ester. The product composition is thus dependent upon the first step along the reaction pathway, i.e., Michael addition.

It has been reported[1] that reaction of **11**[8] and dibenzoylethylene in refluxing EtOH provides after 4 h a hexahydroquinoline of type **5** in 65% yield whereas a tetrahydroindole of type **4** is the principal product when the reaction time is extended to 48 h. In HOAc, even after short reaction times (4 h), the major product is a tetrahydroindole (**4**). These results would appear to indicate that five-membered ring formation is the thermodynamically favored process whereas six-membered ring formation can be kinetically favored. Based on these findings,[1] reaction of **8** and **11** would have been expected to provide compound **14** under acidic conditions. Exposure of vinylogous amide **11** to unsaturated keto ester **8** under nitrogen in refluxing pyridine or HOAc led only to hexahydroquinoline **12**, which could be easily oxidized to tetrahydro-

Scheme III



quinoline **13**. None of the isomeric tetrahydroindole **14** was isolated or even observed under either acidic or neutral reaction conditions. When hexahydroquinoline (**12**) was heated for several days under N_2 in either EtOH or HOAc it remained unchanged. In refluxing aqueous HOAc **12** underwent oxi-

dation to **13**. Vinylogous amide **11** clearly prefers to undergo conjugate addition 1,4 to the ketone under basic, neutral, and even acidic reaction conditions. In contrast, the reaction between enamino ketone **7** and **8** is greatly affected by solvent conditions. These findings that enamino ketones **7** and **11** should behave differently toward unsaturated keto ester **8** cannot yet be accounted for.

With the exception of those products resulting from decomposition or dimerization of starting material (30–50%) no products other than those reported could be isolated. In none of the reactions discussed was any attempt made to maximize yields. Experiments involving the use of other vinylogous amides of general structure **1** and other unsymmetrical diacylethylenes (**2**) are currently in progress. The stereochemistry of substituents about the ethylene bond of the unsaturated keto ester is a factor which significantly influences the course of such reactions and one which will also be discussed in future publications.

Experimental Section

The IR spectra were recorded on a Perkin-Elmer Model 257 or 457 grating spectrophotometer and NMR spectra were recorded using either a Varian T-60 or EM-360 spectrometer. ^{13}C NMR spectra were recorded using a Varian XLFT-100 spectrometer as were the 100-MHz NMR spectra. Chemical shifts (δ) are recorded relative to Me_4Si; coupling constants (J) are given in hertz. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The UV spectra were obtained on a Cary Model 16 spectrophotometer. In all workup procedures, the drying process involved swirling over $MgSO_4$ and filtering prior to evaluation.

Methyl 3-Pivaloylacrylate (8).[5c] **A. 3-Pivaloyllactic Acid.** Glyoxylic acid hydrate (38.0 g, 0.41 mol) in aqueous MeOH (1:1) (2 L) was added dropwise to a solution of pinacolone (34.0 g, 0.34 mol) in H_2O (300 mL). After the addition of a solution of NaOH (27.0 g, 0.67 mol) in H_2O (60 mL), the mixture was allowed to stir at ambient temperature for 24 h, then poured into H_2O (3 L) and washed with Et_2O. The aqueous layer was acidified with concentrated HCl to pH 3 and extracted thoroughly with Et_2O. These latter Et_2O extracts were dried and evaporated to give a white solid which on recrystallization from petroleum ether provided 17.8 g (30%) of 3-pivaloyllactic acid as white crystals: mp 55–57 °C; NMR ($CDCl_3$) δ 1.10 (s, 9 H), 2.96 (AB q, J = 2, 5 Hz, 1 H), 3.10 (d, J = 5 Hz, 1 H), 3.27 (s, 1 H), 4.30 (AB q, J = 5, 5 Hz, ½ H), 4.59 (t, J = 5 Hz, ½ H), and 7.95 (broad s, exchangeable, 1 H); IR (CH_2Cl_2) 3650–2400, 1715 with shoulder at 1700 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_4$: C, 55.2; H, 8.1. Found: C, 55.0; H, 7.9.

B. Methyl 3-Pivaloyllactate. A suspension of 3-pivaloyllactic acid (17.4 g, 0.1 mol), $NaHCO_3$ (9.3 g, 0.11 mol), and MeI (32 g, 0.225 mol) in DMA (125 mL) was stirred in the dark for 18 h, then poured onto H_2O (1 L). The resulting mixture was extracted with Et_2O and the combined extracts washed with brine, dried, and evaporated to give 18.0 g (96%) of crude methyl 3-pivaloyllactate as a yellow oil: NMR ($CDCl_3$) δ 1.09 (s, 9 H), 2.83–3.06 (m, 2 H), 3.22 (s, 1 H), 3.76 (s, 3 H), 4.27 (AB q, J = 5, 5 Hz, ½ H), and 4.51 (t, J = 5 Hz, ½ H); IR (CH_2Cl_2) 3540 (broad), 1750 and 1715 cm^{-1}.

C. Methyl 3-Pivaloylacrylate (8). In a flask equipped with a Dean-Stark trap, a solution of methyl 3-pivaloyllactate (18.0 g, 0.096 mol) and p-TsOH (0.2 g) in xylene (300 mL) was heated at reflux for 18 h. Evaporation of the solvent was followed by filtration of a $CHCl_3$ solution of the residue through silica gel (450 g) using 2% MeOH/$CHCl_3$ (12 L) as elutant. Distillation of the crude keto ester 8 (14.0 g) obtained by evaporation of the elutant gave 9.0 g (55%) of 8 as a yellow oil: bp 65–70 °C (0.1 mm); NMR ($CDCl_3$) δ 1.11 (s, 9 H), 3.82 (s, 3 H), 6.74 (d, J = 16 Hz, 1 H), and 7.53 (d, J = 16 Hz, 1 H); IR (CH_2Cl_2) 1735 and 1695 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.5; H, 8.3. Found: C, 64.0; H, 8.2.

Methyl 1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-7-(dimethylethyl)pyrido[2,3-*d*]pyrimidine-5-carboxylate (10a). A continuous stream of dry air[9] was passed through a refluxing solution of unsaturated keto ester **8** (1.70 g, 10 mmol) and 6-amino-1,3-dimethyluracil (**7**, 1.55 g, 10 mmol) in pyridine (45 mL) for 12 h. After cooling, the mixture was evaporated to dryness and the residue dissolved in $CHCl_3$ and filtered through silica gel (300 g). Elution with $CHCl_3$ (2 L) provided a white, crystalline material on evaporation of the solvent. Recrystallization from a minimum of Et_2O gave 1.1 g (36%) of **10a** as white crystals: mp 109.5–111 °C; NMR (XL-100) ($CDCl_3$) δ 1.41 (s, 9 H), 3.42 (s, 3 H), 3.73 (s, 3 H), 4.01 (s, 3 H), and 7.16 (s, 1 H); IR ($CHCl_3$) 1745, 1715, and 1670 cm^{-1}.

Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.0; H, 6.3, N, 13.8. Found: C, 59.0; H, 6.2; N, 13.6.

Methyl 6-(Dimethylethyl)-2,3,4,5-tetrahydro-1,3-dimethyl-2,4-dioxo-1*H*-pyrolo[2,3-*d*]pyrimidine-5-acetate (9a). To a solution of unsaturated keto ester **7** (10.2 g, 0.06 mol) in EtOH (200 mL) was added aminouracil **8** (9.3 g, 0.06 mol) and the mixture was heated at reflux for 16 h, then cooled to ambient temperature and filtered. Evaporation of the filtrate provided a white solid, which on recrystallization from a minimum of Et_2O gave 2.5 g (14%) of **9a**: mp 144–146 °C; NMR (XL-100) ($CDCl_3$) δ 1.25 (s, 9 H), 2.32 (AB q, J = 9, 15 Hz, 1 H), 3.22 (AB q, J = 3, 15 Hz, 1 H), 3.39 (s, 3 H), 3.57 (s, 3 H), 3.69 (s, 3 H), and 3.85 (AB q, J = 3, 9 Hz, 1 H); IR ($CHCl_3$) 1740, 1710, 1660, and 1600 cm^{-1}; UV (EtOH) 325 nm (ϵ 4273) and 218 (14 079).

Anal. Calcd for $C_{15}H_{21}N_3O_4$: C, 58.6; H, 6.9; N, 13.7. Found: C, 58.8; H, 7.1; N, 13.2.

Methyl 2-(Dimethylethyl)-1,4,5,6,7,8-hexahydro-5-oxoquinoline-4-carboxylate (12). A solution of vinylogous amide **11**[8] (11.1 g, 0.1 mol) and unsaturated keto ester **8** (17.0 g, 0.1 mol) in HOAc (150 mL) was heated at reflux under N_2 for 48 h. Evaporation of the solvent and partition of the residue between Et_2O and saturated aqueous $NaHCO_3$ provided, after evaporation of the brine-washed Et_2O phase, an oil of one spot purity which crystallized on standing. Trituration with a minimum of Et_2O gave 9.56 g (36.3%) of **12** as white crystals: mp 172–174 °C; NMR)cdcl$_3$) δ 1.10 (s, 9 H), 1.84–2.60 (m, 6 H), 3.64 (s, 3 H), 4.25 (d, J = 4 Hz, 1 H), 4.65 (d of d, J = 1.5, 4 Hz, 1 H), and 6.42 (broad s, exchangeable, 1 H); IR ($CHCl_3$) 3455, 1740, 1680 (w), and 1620 cm^{-1}; UV (EtOH) 343 nm (ϵ 3873), 233 (4052), and 214 (4039).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.4; H, 8.0; N, 5.3. Found: C, 68.2; N, 8.0; N, 5.2.

Methyl 2-(Dimethylethyl)-5,6,7,8-tetrahydro-5-oxoquinoline-4-carboxylate (13). A. From 12. To a solution of hexahydroquinoline **12** (9.15 g, 0.035 mol) in xylene (500 mL) was added 10% Pd/C (0.5 g) and the suspension was heated at reflux for 18 h. After filtration through Celite, evaporation of the filtrate gave a white solid. Recrystallization from Et_2O afforded 4.0 g (44%) of tetrahydropyridine **13**: mp 139.5–40.5 °C; NMR ($CDCl_3$) δ 1.34 (s, 9 H), 2.19 (d of q, J = 6 Hz, 2 H), 2.67 (broad t, J = 6 Hz, 2 H), 3.22 (broad t, J = 6 Hz, 2 H), 3.96 (s, 3 H), and 7.22 (s, 1 H); IR ($CHCl_3$) 1740 and 1690 cm^{-1}; UV (EtOH) 283 nm (ϵ 3632) and 233 (3680).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.3; N, 5.4. Found: C, 69.2; H, 7.5; N, 5.3.

B. From 8. Following the procedure described to prepare **10a**, but using vinylogous amide **11** in place of **7**, gave a 24% yield of **13**, mp 138.5–140 °C.

Acknowledgment. Those services provided by the Analytical Section of the Medicinal Chemistry Department are gratefully acknowledged. In particular the ^{13}C NMR calculations of Ms. R. Mansukhani are appreciated.

Registry No.—**7**, 6642-31-5; **8**, 34553-31-6; **9a**, 61689-27-8; **10a**, 61689-28-9; **11**, 5220-49-5; **12**, 61689-29-0; **13**, 61689-30-3; glyoxylic acid, 298-12-4; pinacolone, 75-97-8; 3-pivaloyllactic acid, 61689-31-4; MeI, 14-88-4; methyl 3-pivaloyllactic acid, 61689-32-5.

References and Notes

(1) Y. Tamura, Y. Sakaguchi, T. Kawasaki, and Y. Kita, *Heterocycles*, **2**, 645 (1974); **3**, 183 (1975). For other examples of the reaction between enamino ketones and unsaturated dicarbonyl compounds, see M. Pfau and C. Ribiere, *Bull. Soc. Chim. Fr.*, 776 (1976), and references cited therein.

(2) One reviewer suggested that the possibility of Michael addition of the enamino ketone nitrogen to the double bond of the biscarbonyl ethylene followed by annelation be considered. We had, based on our previous work[6] involving the reactivity of these bidentate systems under neutral reaction conditions, ignored that possibility.

(3) N. El-Ghandour, O. H. Rousseau, and J. Soulier, *Bull. Soc. Chim. Fr.*, 2817 (1972).

(4) (a) N. Sugiyama, T. Gasha, K. Kataoka, and C. Kashima, *Bull. Chem. Soc. Jpn.*, **41**, 2219 (1968); **42**, 1098 (1969); (b) N. Hellstrom and S. Gronowitz, *Lantbrukshoegsk. Ann.*, **25**, 363 (1959); *Chem. Abstr.*, **54**, 9751*f* (1960).

(5) For other preparations of unsaturated keto esters see (a) J. Schreiber, C.-G. Wermuth, and A. Meyer, *Bull. Soc. Chim. Fr.*, 625 (1973), and references cited therein; (b) T. Kametani, H. Ague, K. Saito, and K. Fukumoto, *J. Heterocycl. Chem.*, **6**, 453 (1969); (c) G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1367 (1970).

(6) G. B. Bennett, W. R. J. Simpson, R. B. Mason, R. J. Strohschein, and R. Mansukhani, *J. Org. Chem.*, **42**. 221 (1977).

(7) While the yields reported are quite low and no attempt was made at opti-

mization, every effort was made to ensure that, other than those products resulting from decomposition of the starting materials,[10] no reaction products isomeric with those isolated were present in the crude reaction-product mixtures. In all cases greater than 95% of the material balance has been accounted for.

(8) F. Zymalkowski and J. Rimek, *Naturwissenschaften*, **47**, 83 (1960).
(9) The air was dried by passage through successive drying towers of concentrated H_2SO_4, solid KOH, and silica gel.
(10) Cf. E. L. Esmans and F. C. Alderweireldt, *Bull. Soc. Chim. Belg.*, **82**, 435 (1973).

The Effect of Lewis Acids on Stereoselectivities in Ketone Reductions. The Principle of Complexation-Induced Conformational Perturbation. Energy Minimization in the Transition States for Hydride Transfer[1]

Michael P. Doyle,*[2a] Charles C. McOsker,[2b] Nancy Ball, and Charles T. West

Department of Chemistry, Hope College, Holland, Michigan 49423

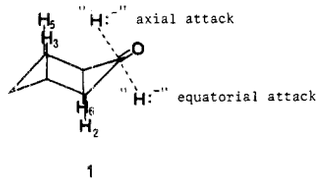
Received September 30, 1976

Stereochemical results from reductions of alkyl-substituted cyclohexanones by organosilanes in boron trifluoride etherate and in aqueous sulfuric acid demonstrate that Lewis acid complexation with the carbonyl oxygen plays a major role in determining product stereoselectivity. These results, together with similar changes in stereoselectivity due to variations in the metal ion employed in Meerwein–Ponndorf–Verley, borohydride, and aluminum hydride reductions, lead to the proposal that stereoselectivity in ketone reductions is a function of the size of the complexing agent and the degree of association between the carbonyl oxygen and the complexing agent in the transition state for hydride transfer. To explain the "4-methyl, 4-*tert*-butyl effect" and the "2-methyl effect" the principle of complexation-induced conformational perturbation is introduced. According to this tenet, the reacting complexed ketone adopts a conformation that minimizes steric (or torsional) interactions in the transition state for hydride transfer. Stereochemical and kinetic data are consistently explained by application of this principle. Stereochemical results from reductions of model ketones, *trans*-1-decalone and *trans*-2-decalone, are reported; these results are consistent with the transition state model for complexation-induced conformational perturbation but are opposite to those predicted from the conformational equilibrium model. The effects of the postulate that hydride transfer preferentially occurs to minimize interactions between the incoming hydride and the complexed ketone on the currently held models for stereoselectivity in nucleophilic addition reactions are discussed.

The predominance of one stereoisomeric product in nucleophilic additions to ketones depends on the nature of the nucleophile, on the stereochemical relationship between the reactants during addition, and on the intricate details of the reaction pathway.[3] The evolution of current understanding of stereoselectivity in these reactions has occurred primarily through studies of cyclic ketones.[4,5] A wealth of data on stereoselective hydride reductions of cyclic ketones exists and is interpreted with general acceptance[5] in terms of a combination of steric and torsional interactions between the substrate and the reducing agent in the transition state for hydride transfer as well as by electronic influences emanating from polar substituents remote from the carbonyl group. Conformational[6] and molecular orbital[7] influences on stereoselectivity in cyclic ketone reductions have recently been proposed.

Steric approach control,[4b] which implies that the transition state resembles the reactants in geometry, is widely believed to govern the course of ketone reductions by hydride reducing agents. Furthermore, hydride transfer is understood to preferentially occur when the ketone is in its most stable conformation and, to effect maximum overlap in the transition state, hydride approaches the carbonyl carbon along a line perpendicular to the plane of the carbonyl group.[7e,8]

When these criteria are applied to reductions of substituted cyclohexanones, for example, a distinct picture of stereoselective control emerges (structure 1). Axial hydride attack is subject to steric interactions from atoms or groups of atoms on the axial 3,5 positions. Equatorial hydride attack is subject to torsional interference with the axial 2,6 hydrogens. The stereoselectivity of hydride transfer to substituted cyclohexanones is believed to be determined by the relative magnitude of these steric and torsional interactions.[5]



1

Recent stereochemical data on reductions of cyclohexanones by numerous aluminum hydride,[4h,9] borohydride,[10] and organosilane[1,6d,11] reagents have generated several questions that cannot be explained by the account of stereoselective control outlined in structure **1**. The "2-methyl effect",[6a] in which the relative yields of the less stable cis isomer from reductions of 2-methylcyclohexanone are substantially greater than those from 4-*tert*-butylcyclohexanone, requires modification of the currently held view of stereoselectivity. The complex "4-methyl, 4-*tert*-butyl effect" is even more difficult to understand. Here, the relative yield of the less stable cis alcohol from reductions of 4-methylcyclohexanone is greater than that from 4-*tert*-butylcyclohexanone when sterically small reducing agents are employed, but this phenomenon is reversed when sterically large reducing agents are used.

In the course of our investigations of stereoselectivity in ketone reductions by organosilanes we have found that the nature of the Lewis acid catalyst has a major effect.[1] In this paper we assign to Lewis acid complexation an integral role in the control of reduction stereoselectivity. We will describe the stereochemical relationship between the reactants in the process of reduction in terms of "complexation-induced conformational perturbation" of the ketone in the transition state. This new principle of stereoselective control unravels the "2-methyl effect" and the "4-methyl, 4-*tert*-butyl effect", satisfactorily explains the results from hydride reductions and nucleophilic additions of cyclic ketones, and predicts the stereochemical course of these reactions more successfully than previous theories.