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Richard R. Schrock, John A. Osborn*
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
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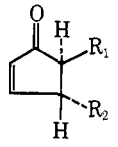
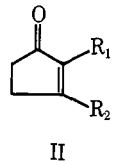
A Versatile Synthesis of Cyclopentenones

Sir:

Δ^2-Cyclopentenones with vicinal disubstitution adjacent to the carbonyl function and away from the double bond (*e.g.*, I) are potentially versatile intermediates not only as such, but also because they can be



I

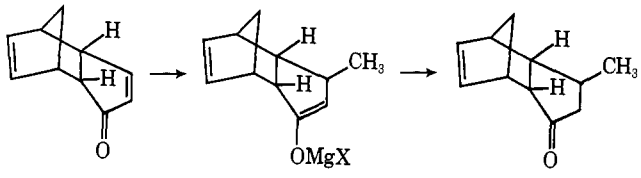


II

expected to equilibrate under a variety of circumstances to the (more stable) other α,β-unsaturated ketone (*e.g.*, II).[1]

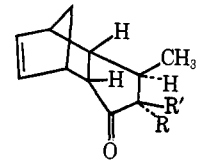
We now report a synthesis of cyclopentenones of type I and their interconversion to II *via* the smooth thermal cracking of formal adducts of 1, *e.g.*, VIIb → VIIIb (*vide infra*).

The ketone III, readily available from dicyclopentadiene by oxidation with selenium dioxide followed by further oxidation of the allylic alcohol[2] (most efficiently with Jones' reagent), easily undergoes cuprous ion catalyzed addition of Grignard reagents. Addition of methylmagnesium halide thus leads to the expected V.[3] Initial attempts at interception of the intermediate enolate[4] IV with reactive halides (allyl bromide, methyl iodide) led, surprisingly, to mixtures containing appreciable amounts of α-dialkylated material. For in-



III IV V

stance, replacement of the ether solvent after formation of IV by a 1:1 mixture of tetrahydrofuran–hexamethylphosphoramide and addition of 30% excess of methyl iodide, followed by 8–10 hr of stirring at room temperature and 5 hr of refluxing gave 90% yield of a mixture of 85% of the *trans*-dimethyl ketone VI (R = CH_3, R′ = H) and 15% of the dimethyl derivative VI (R = R′ = CH_3). Similarly, using allyl bromide as the alkylating agent, 50% of the VI (R = allyl, R′ = H) and 20% of the diallylated compound (R = R′ = allyl) were obtained. Not surprisingly, metallic enolates, *e.g.*, lithium, sodium, which undergo more rapid proton transfer than magnesium enolates lead to even larger amounts of α-dialkylation. We have

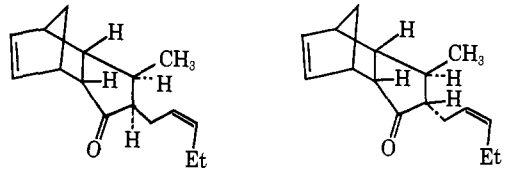


VI

obtained evidence, based on the study of the alkylation of metalloenamines derived from V (*vide infra*), which allows a rationalization of the somewhat surprising ease with which dialkylation takes place; alkylation takes place largely (exclusively ?) from the exo side, in spite of the interference by the β-methyl group (leading to the kinetic formation of a cis α,β-disubstituted ketone), and the entrance of the second alkyl group is therefore not appreciably more hindered than that of the first.

Complete elimination of the troublesome dialkylation was achieved by using the metalloenamine procedure.[5] The crude cyclohexylimine from V and cyclohexylamine was transformed to the metalloenamine (1 equiv of lithium diisopropylamide—made *in situ* by addition of butyllithium to diisopropylamine in tetrahydrofuran—4.5 hr at room temperature) and the salt was treated with 1 equiv of *cis*-1-chloro-2-pentane[6] in tetrahydrofuran. After 14 hr at room temperature and 3-hr reflux, followed by hydrolysis of the imine (refluxing with sodium acetate–acetic acid–water (1:2:2) for 4 hr), the ketone mixture contained *only* the product VII of monoalkylation, in addition to some starting material. The α-alkylated product VIIa,b was obtained in 62% yield from V after chromatography on silica gel (elution with petroleum ether). Support for the contention above that entry of the alkyl group is from the exo side follows from the determination that the alkylated product thus obtained is a mixture of 53% VIIIa and 47% VIIb.[7]

Equilibration with 10% ethanolic potassium hydroxide (heating 1 hr) transformed the mixture into the essentially pure (>95%) trans isomer VIIb.



VIIa VIIb

(1) For another synthesis of cyclopentenones of type I *cf.* D. P. Strike and H. Smith, *Tetrahedron Lett.*, 4393 (1970). These authors' interest in cyclopentenones of type I was related to their relationship to the prostaglandin system, a relationship which was also at the origin of the Columbia group's efforts described here.

(2) K. Alder and F. H. Flock, *Chem. Ber.*, 87, 1916 (1954); M. Rosenblum, *J. Amer. Chem. Soc.*, 79, 3180 (1957).

(3) T. Sakan and K. Abe, *Tetrahedron Lett.*, 2471 (1968).

(4) *Cf.* G. Stork, *Pure Appl. Chem.*, 17, 1383 (1968).

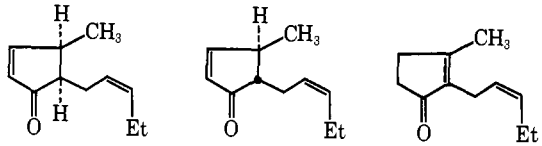
(5) G. Stork and S. Dowd, *J. Amer. Chem. Soc.*, 85, 2178 (1963).

(6) Kindly provided through the courtesy of Dr. W. I. Taylor, International Flavors and Fragrances, Union Beach, N. J.

(7) Determined by vpc analysis (Carbowax, 155°) after cracking to VIIIa, b; VIIIa has the shorter retention time. We believe that considerable equilibration takes place during the hydrolysis of the imine and that the kinetic product may well be exclusively cis. This view receives support from the observation that alkylation can become very difficult with ketones such as V in which groups much larger than methyl are present on the β carbon (observations by Dr. Gary Koppel in the Columbia Laboratories). The observation of exclusive trans products from the alkylation of enolates of V reflects, we believe, the much faster proton transfers with these enolates than with metalloenamines, transfers which are, of course, responsible for polyalkylation.

Completion of the cyclopentenone synthesis required a study of optimum conditions for the retro Diels–Alder reaction. In particular, we were interested in defining conditions which would lead cleanly to cyclopentenones of type I, with no migration of the double bond. Of course, if only the rearranged cyclopentenones (*cf.* II) are required, the position of the double bond after cracking, as well as the stereoisomeric composition of the alkylated mixture (*e.g.*, VIIa–VIIb), would both be inconsequential. It was found, after much experimentation, that while atmospheric pressure distillation, or heating in sealed quartz or Pyrex tubes gave mixtures of I and II, *it is possible to obtain pure cyclopentenones of type I in quantitative yields by slow addition of the "adducts"* (*e.g.*, V, VI, VIIa,b) at the top of a quartz column filled with quartz chips and maintained at 600° while the system is kept under ~0.2 mm (the pyrolysate is collected in a Dry Ice cooled flask). In this manner, a number of pure cyclopentenones of type I were obtained, *e.g.*, I (R_1 = H, R_2 = CH_3[8]), I (R_1 = R_2 = CH_3), and I (R_1 = *cis*-2-pentenyl, R_2 = CH_3), free from the isomeric II, as easily shown by nmr: characteristic α and β vinyl protons in I at δ ~6.0 and 7.4–7.5 (1 H each, d of d, $J_{\alpha,\beta}$ = 6 Hz) and doublet due to 4-methyl group at δ ~1.2 (J = 7 Hz) changing in the isomeric II, R_2 = CH_3, to δ 2.1.

Isomerization to the more stable isomer II could be effected in a variety of ways such as heating with acid,[8] or in sealed Pyrex tubes (220°, 1 hr). Aqueous base isomerization is often convenient. Refluxing with 0.5% aqueous potassium hydroxide for 2 hr of either the trans isomer VIIIb (from VIIb) or of the mixture from VIIa,b gave in about 85% yield (~50% overall from V) *cis*-jasmone IX identical (ir, nmr, uv, mass spectrum, vpc) with an authentic sample.[9,10]



VIIIa VIIIb IX

(8) *Cf.* G. W. Cavill, B. S. Goodrich, and D. G. Laing, *Aust. J. Chem.*, 23, 83 (1970).

(9) *Cf., inter alia*, G. Stork and R. Borch, *J. Amer. Chem. Soc.*, 86, 936 (1964).

(10) The group at Columbia wishes to thank the National Science Foundation and the National Institutes of Health for partial support of this work.

Gilbert Stork,* George L. Nelson
Department of Chemistry, Columbia University
New York, New York 10027

Francis Rouessac, Olivier Gringore
Centre Universitaire du Mans
Le Mans, France

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Calorimetric Measurements on the "Normal" Temperature-Induced Helix–Coil Transition of Poly(N-γ-carbobenzoxy-L-α,γ-diaminobutyric acid)

Sir:

The enthalpy of the helix-to-coil transition of a number of homo- and copolypeptides in the mixed solvent system dichloroethane–dichloroacetic acid (DCE–DCA) is substantially independent of the nature of the side chains. The process is exothermic and its ΔH value, deduced from calorimetric experiments, is in neighborhood of 600–650 cal/mol of residue.[1-4]

The right-handed helical conformation of all polypeptides studied to date is stabilized in DCA–DCE by increasing the temperature.[5]

Poly(N-γ-carbobenzoxy-L-α,γ-diaminobutyric acid) is the only exception.[6] As demonstrated from recent ORD experiments in Yang's laboratory, the temperature-induced helix-to-coil transition of this polypeptide shows "normal" behavior; *i.e.*, its helical state is reached only by lowering the temperature from 30 to about −30°.[7] We have applied the heat of solution calorimetric method[1-3,8] to the study of this system and to its higher homolog poly(N-δ-carbobenzoxy-L-ornithine) (PCBO).

First, we have confirmed Yang's results in the solvent system DCA–DCE that we have used in all previous calorimetric experiments. As usual, in the case of PCBO, we observed an "inverted" temperature-induced helix-to-coil transition. At room temperature and 37% (vol) DCA, a high-molecular-weight sample existed as a solvated random coil (b_0 = 0) and, upon heating, a transition to the helix (b_0 = −600 at 75°) occurred between 30 and 75°.

On the other hand, for a high-molecular-weight PCBBA sample,[9] at 55% (vol) DCA, the transition was "normal" and completed within a temperature range larger than that of PCBO. The random-coil conformation at 80° ($b_0 \simeq 0$) was partially changed into helix by lowering the temperature (b_0 = −340 at 30°).

Figure 1 shows the results of the heat of solution measurements. The change of behavior in going from PCBO to PCBBA is dramatic.

The first part of the ΔH_{sol} curve of PCBO (low DCA content) shows the usual saturation trend which we have associated with side-chain solvation by dichloroacetic acid.[2] At higher DCA content, the sharp change of the solution enthalpy value, occurring at the same DCA concentration as the jump in optical activity, is due to the order–disorder heat effect of an exothermic process (650 cal/mol of residue).

On the other hand, the ΔH_{sol} curve of PCBBA at low DCA content shows only a slight linear variation, having, in addition, opposite sign to those of all other polypeptides investigated.

At 40% (vol) DCA, we observe a sudden change in the ΔH_{sol} corresponding to an exothermic process similar to that observed for PCBO, immediately fol-

(1) G. Giacometti in "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Ed., W. H. Freeman, London, 1968, pp 67–76.

(2) G. Giacometti, A. Turolla, and R. Boni, *Biopolymers*, 6, 441 (1968).

(3) G. Giacometti, A. Turolla, and R. Boni, *ibid.*, 9, 979 (1970).

(4) A. Kagemoto and R. Fujishiro, *ibid.*, 6, 1753 (1968).

(5) G. D. Fasman in "Poly-α-Amino Acids," G. D. Fasman, Ed., Marcel Dekker, New York, N. Y., 1967, Chapter 11.

(6) Another "normal" temperature-induced helix-to-coil transition is that found by Y. Hayashi, *et al.*, *Biopolymers*, 8, 403 (1969), in a study of poly(β-benzyl L-aspartate) in *m*-cresol. In this case, however, the L-polypeptide has a left-handed helical structure.

(7) F. Gaskin, S. Kubota, and J. T. Yang, *J. Amer. Chem. Soc.*, **91**, 6526 (1969).

(8) G. Giacometti and A. Turolla, *Z. Phys. Chem.* (*Frankfurt am Main*), **51**, 108 (1966).

(9) Details on this synthesis will be reported elsewhere.