Tetrahedron Letters No.21, pp. 1337-1343, 1964. Pergamon Press Ltd.
Printed in Great Britain.

THE STRUCTURE AND STEREOCHEMISTRY OF SOME CONDENSATION PRODUCTS OF PULEGONE*

YUAN-LANG CHOW

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ALBERTA, EDMONTON,
ALBERTA, CANADA

(Received 14 February 1964; in revised form 7 April 1964)

Recent interest in the conformational aspects and kinetic behavior of the bicyclo[3,3,1]nonenone system[1] prompts the Author to communicate some abnormal reactions of a pulegone derivative. In a previous communication we have described the condensation of pulegone with ethyl malonate and ethyl acetoacetate[2]. The pulegene acetone so obtained was assigned structure I. The present communication discusses the chemistry of the second product obtained from acetoacetate condensation under acidic conditions ($ZnCl_2$-AcOH), which is now shown to possess the structure and conformation depicted in II.

Compound II, $C_{16}H_{24}O_3$, m.p. 37-39°, $[\alpha]_D = +47.8°$, possesses the following spectral properties; ν_{max} at 1712 and 1635 cm^{-1}, both strong, λ_{max} at 206 mμ (ε, 5900) and 272 (2500)

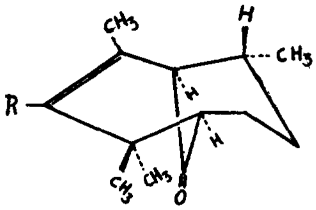
---

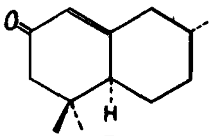
* Presented in part at the Joint Symposium on Chemistry and Industry, Royal Institute of Chemistry (Malayan Section), Singapore, March 8, 1963.

and N.M.R signals at 8.99 τ (doublet, J = 4.5 cps) for a methyl group attached to a secondary carbon, 8.73 and 8.76 τ (two singlets) for gem-dimethyl protons, 8.05 (singlet) for allylic methyl protons and 8.7 τ (triplet) and 5.79 τ (quartet, J = 7 cps) for ethoxy protons. Treatment of II with Brady's reagent gave, instead of the expected hydrazone, the corresponding 2,4-dinitrophenylhydrazide, $C_{20}H_{24}N_4O_6$, m.p. 178-181°, λ_{max} at 326 mμ (ε, 17 700) and ν_{max} at 1700 cm^{-1}. Under the conditions of the initial condensation II rearranges to I. Prolonged hydrogenation in the presence of platinum oxide gave an oily dihydro derivative III, ν_{max} at 1735 and 1715 cm^{-1} and no U.V. maximum above 200 mμ.

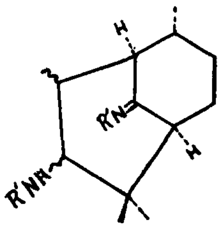
Only the ester group was reduced, when II was refluxed with lithium aluminium hydride in ether for 24 hours. The resulting ketol IV, $C_{14}H_{22}O_2$, had m.p. 80-82.5°, $[\alpha]_D$ = +62.5°, ν_{max} (in CCl_4) at 3640, 1710 and 1665 cm^{-1}, λ_{max} 237 mμ (ε, 2660), 285 (20) and N.M.R. signals for the new hydroxyl carrying methylene protons at 5.82 τ (singlet equivalent to two protons)[3] among others. That only the carboxylate group was reduced in II was further demonstrated by CrO_3-pyridine oxidation of IV followed by air oxidation of the crude aldehyde (ν_{max} in liquid film at 1712, 1660 and 1615 cm^{-1}) to the ketocarboxylic acid V, $C_{14}H_{20}O_3$, m.p. 205-206° (gas evolution), ν_{max} 1718, 1661, 1623 and 1603 cm^{-1} and λ_{max} 270 mμ (ε, 2600), which was also obtained from II by vigorous hydrolysis. Compound V was re-esterfied to II by treatment with thionyl chloride followed by ethanol-pyridine, thus proving that there was no skeletal rearrangment during hydrolysis, or reduction.

The above evidence indicates that compound II contains an α,β-unsaturated carboxylate and simple ketone groups, which are





I



II; R= $-CO_2Et$
IV; R= $-CH_2OH$
V; R= $-CO_2H$
VI: R= -H

VII:R' = $-NH-C_6H_3-2,4-(NO_2)_2$

related in such a way that the double bond is located at the β,γ-position to the ketone group (vide infra). Taking into account the mode of formation of I[1], the isomerization from II to I and the necessity of accommodating the N.M.R. spectral data, the 9-ketobicyclo[3,3,1]nona-2(3)-ene system as shown in II is the only feasible structure for the compound. That the keto group is flanked by both bridge heads is confirmed by i) the failure of the β,γ-double bond to migrate into conjugation with the keto group under vigorous basic hydrolysis of II[4] and ii) the fact that on treatment with NaOD-D_2O solution there was no incorporation of deuterium by the keto acid as shown by mass spectrometry.*

The keto acid V loses one molecule of carbon dioxide rapidly on refluxing in quinoline solution to give the β,γ-unsaturated ketone VI, $C_{13}H_{20}O$, m.p. 33-35°, $[\alpha]_D = +63.9°$, ν_{max} in film at 1715 and 1678 cm^{-1} and λ_{max} at 230 $m\mu$ (ε, 2770) and 286 (142). In the N.M.R. spectrum a quartet equivalent to one proton (J= 1 cps) centered at 5.82τ (coupled with the allylic methyl protons at 8.33τ) substantiates the assignment of the structure. The significant chemical shift to high field of the olefinic proton (ca. 1 ppm above that normally associated with olefinic protons) suggests that the proton lies in the "shielding cone" of the keto group. The magnitude of this shielding should bear a relation with the conformation of the two groups[5] (*vide infra*).

On treatment with Brady's reagent two equivalents of 2,4-dinitrophenylhydrazine are added to the β,γ-unsaturated ketone VI

---

* The mass spectrum shows strong peaks at M-15 and M-59. The spectrum was obtained through the courtesy of Drs. C. Enzell and R. Rybage, to whom the author is much indebted. The exchangeability of a bridge proton and the sensitivity of detecting exchanged deuterium in a bicyclo compound are discussed; (K. Bieman "Mass Spectrometry", McGraw-Hill Book Co. Inc., New York, 1962, P. 246). The failure to incorporate deuterium renders strong support to a bicyclo[3,3,1]nonenone system (cf: ref. 4).

giving yellow crystals, $C_{25}H_{30}N_8O_8$, m.p. 184-186°, λ_{max} 361 mμ (ε, 30,100) with a shoulder at 320 mμ and Rast molecular weight 601, which are assigned the structure VII. The abnormal addition of 2,4-dinitrophenylhydrazine across a β,γ-double bond does not appear to have been demonstrated previously and necessitates a postulation that the keto group and the β,γ-double bond are sterically disposed in such a way that considerable overlap of the π-orbitals such as the well documented π-orbital interaction in the bicyclo[2,2,1]heptenone and bicyclo[2,2,2] octenone systems is possible.[6,7]

Such a postulation is also suggested by the various spectral data of the derivatives, namely; i) the strong I.R. carbon-carbon double bond absorption for all the derivatives concerned, ii) abnormal U.V. absorption at ca. 270 mμ for the conjugated compounds (II and V) and at ca. 230 mμ for the unconjugated compounds (III and VI)[7] and iii) the abnormal upfield shift of the olefinic proton in the N.M.R. spectrum of VI. This evidence together with that concerning the strongly hindered keto group as evidenced by the metal hydride reduction, and 2,4-dinitrophenylhydrazide formation of II, is sufficiently compelling to suggest a boat-quasi-boat fused bicyclo system as depicted in II as the preferred conformation. II also represents the absolute configuration which follows from the known absolute configuration of pulegone.

Derivatives of the bicyclo[3,3,1]nonanone system are formed frequently as a byproduct in the various types of Robinson annelation reactions to which the present condensation is related[8]. The formation of II in acid catalysed condensation is, therefore, readily understandable mechanistically if one assumes that the rate of acetolysis of the ester group and the rate of bicyclo ring formation are comparable*.

The U.V. spectra and the rotations reported were taken in ethanol, and the I.R. spectra in nujol unless otherwise specified. The N.M.R. spectra were taken with a Varian A-60 spectrometer using TMS as an internal standard. All compounds whose molecular formulae are given showed satisfactory analyses.

Acknowledgment: A part of this work was done in Organisk-kemiska Institutionen, Kungl. Tekniska Högskolan, Stockholm. To the Head of the Institute, Professor H. Erdtman the Author is much indebted for his support and to Miss G. Hammerberg for recording spectra. Thanks are also due to Professor D.H.R. Barton for a stimulating discussion.

---

* The acetolysis followed by rapid decarboxylation is assumed to precede the ring closure leading to I since considerable resistance to the acetolysis is to be expected if the ring is closed first.

REFERENCES

1. J. Martin and W. Parker, "The Abstract of the XIXth International Congress of Pure and Applied Chemistry, Division A" London, P. 137, 1963.

2. Y.L. Chow, *Acta Chem. Scand.*, **16**, 205 (1962): Cf P. Wolinsky and M. Ann Tyrell, *Chem. & Ind.*, 1104 (1960).

3. Allylic methylene protons in an allyl alcoholic system give a signal ranging from 5.85 - 5.87τ(cf: Varian N.M.R. Spectral data, Nos. 34, 279, 346 and 367).

4. Cf. V. Prelog. P. Barman and M. Zimmerman, *Helv. Chim. Acta*, **32**, 1284 (1949).

5. W.A. Ayer, C. E. McDonald and J.B. Stothers, *Canada. J. Chem.* **41**, 1113 (1963); H. M. McConnell, *J. Chem. Phys.* **27**, 226 (1957).

6. R.C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956); H. Birnbaum, R. C. Cookson and N. Lewin, *ibid.*, 1225 (1961); S.F. Mason, *ibid.*, 3285 (1962); H. Labhart and G. Wagniere, *Helv. Chem. Acta*, **42**, 2219 (1959).

7. Cf. T. F. Mason, *Quart. Rev.*, **15**, 287 (1961);

8. W.S. Johnson, J.J. Korst, R.A. Clement and J. Dutla, *J. Am. Chem. Soc.*, **82**, 614 (1960); G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkowics, and R. Terrell, *ibid.*, **85**, 207 (1963).