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The Relative Stabilities of *cis* and *trans* Isomers. IV. The 3,5-Dimethylcycloheptanones[1,2]

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The pure *cis*- and *trans*-3,5-dimethylcycloheptanones have been prepared and equilibrated as a test of the applicability of the *conformational rule* to compounds containing a seven-membered ring. The *trans* isomer has the higher refractive index and density and in accordance with the rule was converted largely to the *cis* isomer upon equilibration. For this reaction the constants were $\Delta H^{510} = -800$ cal./mole and $\Delta S^{510} = +0.4$ e.u.

Introduction

Previous studies[2,5] have indicated that the relative molecular volumes, and related properties, of *cis* and *trans* isomers can be predicted by application of either the *dipole rule* or the *conformational rule* depending on the kind of molecule involved. The dipole rule was shown to apply to olefins where the isomerism about a π-electron system yielded a difference in the dipole moments of the isomers, while the conformational rule applied to the cyclic systems which had been studied and which consisted for the most part of five- and six-membered rings. The conformational rule states that the isomer with the lower heat content will have the larger molecular volume.[2] It was predicted earlier[6] that the rule would apply equally well to a wide variety of other structures and, in particular, to both larger and smaller rings. There is no report in the literature of heat contents having been determined for a pair of *cis–trans* isomers in which the ring is larger than six membered. Hence, as a test of the applicability of the conformational rule to such systems, it would be instructive to seek examples of pairs of isomers for which the molecular volumes and the difference in heat contents could be determined. For conformational purposes we may consider that the seven-membered ring possesses the properties of a slightly distorted six-membered ring. Examination of molecular models shows that there are positions in the seven-membered ring which correspond closely to what in the six-membered ring are axial positions, and others that correspond to equatorial positions. The terms[7] *quasi-axial* (a') and *quasi-equatorial* (e') have been used to describe positions of this type. It may be predicted that as in the six-membered ring there will be a steric advantage to having substituents in the e'-positions, and that this will lead to a greater stability for simple *trans*-1,2- or 1,4- and for *cis*-1,3-dimethylcycloheptanes.

Discussion

The case of 1,3-substitution in the seven-membered ring is the more interesting "non-classical" one. If the *cis* isomer is the more stable it should, from the conformation rule, have the larger molecular volume and consequently the smaller numerical values for the density, refractive index and boiling point.

To test these predictions it was necessary to have both the *cis* and *trans* isomers (with unequivocal stereochemistry) of a 1,3-dimethylcycloheptane compound. The 3,5-dimethylcycloheptanones were chosen for this work since it was expected that they could be easily equilibrated by epimerization in the presence of palladium at elevated temperatures,[8] and the point of equilibrium could be determined by infrared analysis. The choice of the ketones rather than the parent hydrocarbons was made for three reasons. First, as Klyne has pointed out,[9] while an a-methyl on a cyclohexane ring has a heat content greater by about 1.8 kcal. than the e-conformer, introduction of a β-keto group into the cyclohexane ring reduces this difference by about 0.9 kcal. Qualitatively a similar effect may be expected in the seven-membered ring, and of course it is experimentally much easier to accurately measure the point of equilibrium by infrared analysis when the energy difference is smaller, as this increases the relative amount of the minor isomer. Second, in general oxygenated compounds give more and stronger bands in the infrared spectrum than do the corresponding hydrocarbons which simplifies the analysis. Third, the ketones were available because of the synthetic method employed.

The syntheses of the pure compounds are outlined on the flow sheet and are straightforward. The *cis* isomer was prepared by hydrogenation of 3,5-xylenol, followed by oxidation of the resulting alcohol VII to *cis*-3,5-dimethylcyclohexanone (Vb). Although the *trans* isomer was presumably formed here in small amount, the *cis* compound was obtained pure in good yield *via* the semicarbazone or oxime. That this compound was *cis* had been firmly established previously,[10] and that it was obtained pure and free of the *trans* isomer was shown as indicated below. Ring expansion of this ketone with diazomethane gave pure *cis*-3,5-dimethylcycloheptanone (VIb) in 44% yield.

The desired intermediate *trans*-3,5-dimethylcyclohexanone (Va) was reported in the literature[10,11] as having been prepared by oxidation of

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[1] Supported in part by a research grant from the National Science Foundation. Presented at the 131st Meeting of the American Chemical Society in Miami, Fla., April, 1957.

[2] Paper III, THIS JOURNAL, **79**, 3443 (1957).

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[5] N. L. Allinger, THIS JOURNAL, **80**, 1953 (1958).

[6] N. L. Allinger, *Experientia*, **10**, 328 (1954).

[7] A. T. Blomquist and P. R. Taussig, THIS JOURNAL, **79**, 3505 (1957).

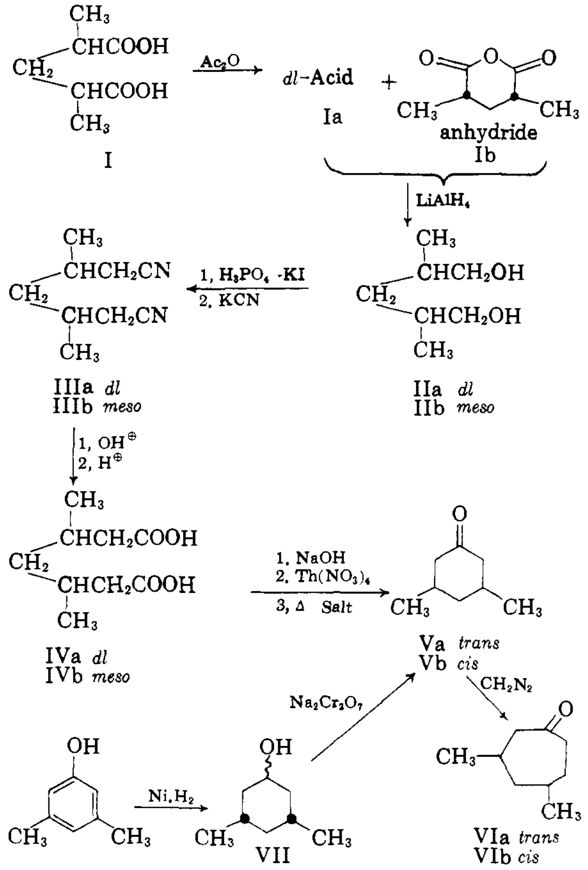
[8] W. E. Bachmann, A. Ross, A. S. Dreiding and P. A. S. Smith, *J. Org. Chem.*, **19**, 222 (1954).

[9] W. Klyne, *Experientia*, **12**, 119 (1956).

[10] J. von Braun and W. Haensel, *Ber.*, **59**, 1999 (1926).

[11] R. Cornubert, H. Lemoine and G. Vivant, *Compt. rend.*, **244**, 1986 (1957).

the corresponding alcohol, which in turn was obtained as a side product in very minor amount in the above-mentioned hydrogenation. The properties of the compound reported were such that the possibility of contamination with the other isomer was difficult to exclude. It was therefore considered essential that the *trans* isomer be prepared in quantity by a method which would not permit the possibility of contamination with the *cis* isomer.



A Michael condensation between ethyl α-bromoisobutyrate and diethyl methylmalonate anion yielded, after hydrolysis and decarboxylation, a diastereomeric mixture of the α,α'-dimethylglutaric acids (I).[12] The separation of the two diastereomers *via* the anhydrides has been described.[13] This procedure was improved so that the *cis*-anhydride Ib was obtained from the mixture in 44% yield, and the *dl*-isomer was obtained as the free acid Ia in a yield of 28%. Since the *dl*-acid was the one most desired, the isomerization of the *meso*-acid to the *dl*-form was investigated. It was found, however, that only 10–15% of pure *dl*-acid could be isolated after such an equilibration.

The *cis*-anhydride and *dl*-acid were separately reduced with lithium aluminum hydride and yielded respectively diols IIb and IIa. No epimerization occurs under these conditions.[14]

The diols were converted to the corresponding diiodides by the excellent method of Stone and Shechter,[15] and these were used directly without purification to prepare the corresponding dinitriles III. The over-all yields of dinitrile from diol were satisfactory, 40–50%. The nitrile IIIa yielded upon hydrolysis the acid IVa which was converted first to its sodium salt, and then to its thorium salt. Pyrolysis of the thorium salt[16] gave a pure sample of *trans*-3,5-dimethylcyclohexanone (Va). A sample of the *cis* isomer Vb was prepared by a Thorpe cyclization of nitrile IIIb and corresponded well in its properties with the *cis* isomer obtained *via* the hydrogenation.

The cyclohexanones V were converted to the corresponding cycloheptanones VI with diazomethane.[17] It is of interest that the *cis* isomer Vb was ring expanded to the cycloheptanone VIb in reasonable yield (52%) similar to that obtained with cycloheptanone itself.[18] The principal side product formed was the oxide, and only a trace of the cyclooctanones was found. On the other hand, under the same conditions the *trans* isomer furnished only an 18% yield of VIa and a considerable amount of the cyclooctanones was formed, a 7% yield of the latter being isolated in pure condition. This small yield reflects in part the difficulty of separating by fractional distillation small amounts of homologous compounds, but the contrast between the two isomers is noteworthy.

Results

The equilibration of the *cis*-and *trans*-3,5-dimethylcycloheptanones was carried out in sealed tubes with a palladium–charcoal catalyst at both 200° and 275°. At each temperature the equilibrium was approached from both sides, and the same *cis*/*trans* ratio was obtained from each starting material. Competing but slow side reactions also occurred, apparently including a dehydrogenation since a new band appeared at 6.25 μ. When the equilibration was carried out by heating the tubes for a minimum amount of time this band was still rather weak, indicating that under these conditions this side reaction was minor. After equilibrium was established, further heating increased the amount of this product but did not change the *cis*/*trans* ratio. Consistent with this interpretation, the sum of the *cis* and *trans* compounds did not add to quite 100%, the total being in the range of 89–97%. Because of the presence of this extraneous material the analysis of the infrared spectra was carried out by the base-line density method.[19] The two bands of analytical use were located at 11.31 (*trans*) and 8.61 μ (*cis*). Synthetic mixtures of the two pure components could be analyzed to within about 1%. The data are summarized in Table I. Unfortunately the accuracy of the infrared analysis is uncertain because of the possibility of a decomposition product absorbing at one of the analytical wave lengths. There were no other strong bands in the spectra suitable for the

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[12] E. Moller, *Ber.*, **43**, 3250 (1910).

[13] K. von Auwers and J. F. Thorpe, *Ann.*, **285**, 310, 315 (1895).

[14] D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950).

[15] H. Stone and H. Schechter, *J. Org. Chem.*, **15**, 491 (1950).

[16] L. Ruzicka and W. Brugger, *Helv. Chim. Acta*, **9**, 339 (1926).

[17] D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 181 (1939).

[18] (a) E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson, THIS JOURNAL, **61**, 1057 (1939); (b) T. J. de Boer and H. J. Backer, *Org. Syntheses*, **34**, 24 (1954).

[19] J. J. Heigl, M. F. Bell and J. U. White, *Anal. Chem.*, **19**, 293 (1947).

analysis which could be used as an accurate check. Other weaker bands agreed with the strong bands used, but these known weak bands were only good to 5–10%.

TABLE I

EQUILIBRATION DATA FOR 3,5-DIMETHYLCYCLOHEPTANONES

	Optical densities					K
473°K.	11.31μ	8.61μ	% *trans*	% *cis*	% total	*cis/trans*
cis	0	0.328				
trans	0.114	0				
Equil. *cis*	.025	0.218	21.9	66.5	88.4	3.04
Equil. *trans*	.027	.241	23.7	73.4	97.1	3.10
548°K.						
cis	0	.330				
trans	0.112	0				
Equil. *cis*	.028	0.222	25.0	67.2	92.2	2.69
Equil. *trans*	.029	.232	25.8	70.2	96.0	2.72

The data summarized in Table II for the reaction *trans*-3,5-dimethylcycloheptanone ⇄ *cis*-3,5-dimethylcycloheptanone were calculated from the equations $-\Delta F = RT \ln K$ and $\Delta F = \Delta H - T\Delta S$. Certain conclusions can be drawn from these data. The energy difference between a methyl group in the *e′-vs. a′*-position in the seven-membered ring is essentially the same as that found in the six-membered ring when the methyl is β to a keto group (800–900 cal.).[9]

TABLE II

THERMODYNAMIC CONSTANTS FOR *trans*-3,5-DIMETHYLCYCLOHEPTANONE ⇄ *cis*-3,5-DIMETHYLCYCLOHEPTANONE

T, °K.	K	$-\Delta F$, cal./mole	$-\Delta H^{510}$, cal./mole	ΔS^{510}, e.u.
473	3.07	1053	864 ± 200	+0.40 ± 0.40
548	2.71	1083		

The conformational rule predicts the correct order[20] for the physical properties of the 3,5-dimethylcycloheptanones. The constants are: *cis*, $n^{25}\text{D}$ 1.4524, d^{25} 0.9115 g./ml., b.p. 204.2° (747 mm.); *trans*, $n^{25}\text{D}$ 1.4572, d^{25} 0.9158 g./ml., b.p. 203.3° (747 mm). The boiling points are within experimental error of one another, and such a close similarity was not anticipated by analogy with the six-membered ring. For example, the difference in boiling point between the *cis* and *trans* isomers of each pair of the dimethylcyclohexanes is 5–6°. The lack of difference in boiling point between isomers of this kind seems to be general for rings larger than six-membered.[21] It unfortunately follows that while *cis–trans* isomers in cyclohexane systems are usually easily separable by fractional distillation or by gas phase chromatography, the corresponding cycloheptane compounds are not so separable.

The entropy value is also informative. If a small number of fixed conformations existed in these compounds as is the case with the cyclohexane derivatives, then because the two isomers would be expected to have conformers of different heat contents there should be a difference in the entropy of mixing of the conformers which make up each isomer.[22] Since the entropy of the reaction is within experimental error of zero, there is no evidence for such a situation. The most probable alternative is to have a large number of conformations of not too different energies. It seems likely that such a situation obtains in all of the cycloalkanes with rings larger than six membered and evidence consistent with this view has been obtained from infrared spectra.[23]

Experimental

α,α′-Dimethylglutaric Acid (I).—The sodium salt of diethyl methylmalonate[24] was allowed to react with ethyl α-bromoisobutyrate, and the resulting ester was converted to a mixture of the stereoisomers of I essentially as described.[13] For separation of the *dl* and *meso* forms of the acid the general procedure used by von Auwers and Thorpe was employed, but with some modification which greatly facilitated the operation.

The acid I, 280 g., was heated at 100° for 1 hr. with 330 ml. of acetic anhydride. Distillation of the reaction product yielded, after a forerun, 245 g. of the mixed *meso*- and *dl*-anhydrides. This material was dissolved in 200 ml. of hot ethyl acetate, and crystallization was allowed to proceed by leaving the solution first at 25° for 12 hr. and then at −20° for 2 hr. The crystals were collected, wt. 135 g. Recrystallization of this material gave 109 g. of pure *meso*-anhydride Ib, m.p. 91.4–92.8°, reported m.p. 94–95°. The combined ethyl acetate solutions were reduced to a volume of 100 ml., and a second crop of crude anhydride (30 g.) was frozen out at −20°. The ethyl acetate solution was diluted with 150 ml. of water, and the resulting two-phase solution was boiled to remove the ethyl acetate. The clear homogeneous solution was then allowed to cool to room temperature, and the crude *dl*-acid, 71 g., m.p. 128–136°, was obtained by filtration. Two recrystallizations of the acid gave pure Ia, wt. 44.5 g., m.p. 139–141°, reported[13] m.p. 140–141°.

The isomerization of the *meso*-anhydride to the *dl*-form was also carried out since the *dl*-isomer was the one mainly desired. The equilibrium proved to be quite unfavorable. Thus, when 153 g. of the pure *meso*-anhydride was equilibrated by boiling for two hours with a solution of 2 g. of sodium in 150 ml. of alcohol followed by addition of 150 g. of potassium hydroxide in 500 ml. of water and an additional 1 hr. of reflux, the acid isolated could be separated as described earlier into 133 g. of crude *meso*-anhydride and 18 g. of the pure *dl*-acid. That an equilibrium point had been reached was shown by a similar isomerization using the diester, which led to similar results.

***dl*-2,4-Dimethyl-1,5-pentanediol (IIa).**—The acid Ia (58 g., 0.362 mole) was added *via* a Soxhlet extractor to a suspension of 25.3 g. (0.724 mole) of lithium aluminum hydride in one liter of dry ether under a nitrogen atmosphere. After an additional hour of stirring, the excess hydride was destroyed by the addition of 10 ml. of ethyl acetate followed by 200 ml. of water and then 300 ml. of 6 *N* hydrochloric acid. Because of the high solubility of the alcohol in water, the solution was extracted ten times with 150-ml. portions of ether. The ether extracts were dried with magnesium sulfate, and the ether was evaporated. The residue was distilled through a two-foot Podbielniak type column and furnished, after an 0.9-g. forerun, 34 g. (71%) of the diol, b.p. 126–128° (5 mm.), $n^{25}\text{D}$ 1.4515.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.59; H, 12.20. Found: C, 63.52; H, 11.97.

***dl*-2,4-Dimethyl-1,5-dicyanopentane (IIIa).**—Diol IIa, 43.5 g., was dissolved in a cooled solution of 42.5 g. of phosphorus pentoxide in 89 ml. of 85% phosphoric acid. After addition of 220 g. of potassium iodide, the mixture was stirred at 115° for 3.5 hr. The cooled mixture was poured into 150 ml. of water, and the solution was extracted with ether. The ether extracts were washed with $Na_2S_2O_3$ solu-

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[20] At least three cases, the isomeric pairs of the methylcyclohexanols, are known in which the more stable isomer definitely has the higher boiling point (E. L. Eliel and R. G. Haber, *J. Org. Chem.*, **23**, in press (1958)), although the conformational rule, which was stated in terms of molecular volume,[3] applies correctly.

[21] S. Greenberg and J. Allinger, unpublished work.

[22] C. W. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1947).

[23] (a) E. Billeter, T. Bürer and H. H. Gunthard, *Helv. Chim. Acta*, **40**, 2046 (1957); (b) T. Bürer and H. H. Gunthard, *ibid.*, **40**, 2054 (1957).

[24] R. F. B. Cox and S. M. McElvain, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 279.

tion and water and were dried. Evaporation of the ether (finally *in vacuo*) left the crude diiodide, wt. 92 g. The iodide was added to a mixture of 65 g. of potassium cyanide in 500 ml. of 70% ethanol, and the resulting mixture was heated under reflux for 64 hr. About 150 ml. of ethanol was then distilled from the mixture, water was added, and the product was extracted with ether. The extracts were dried with magnesium sulfate and the ether was evaporated. Distillation of the residue through a two-foot Podbielniak type column gave, after a forerun of 7.6 g., the dinitrile, b.p. 156–158° (3.5 mm.), wt. 20.4 g. (48% from IIa), $n^{25}D$ 1.4455.

Anal. Calcd. for $C_9H_{14}N_2$: C, 71.97; H, 9.39. Found: C, 72.27; H, 9.28.

dl-β,β′-**Dimethylpimelic Acid (IVa).**—Nitrile IIIa (20.4 g., 0.136 mole) was hydrolyzed with 31 g. (0.54 mole) of potassium hydroxide in 150 ml. of 70% ethanol by heating the solution under reflux for 7 hours. After addition of 100 ml. of water, the ethanol was removed by distillation. The solution was then acidified, and after thorough cooling in ice the crystals were collected, m.p. 138–140°, wt. 21.2 g. (83%). Recrystallization from benzene–acetone gave white plates, m.p. 139.9–140.9°.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.64; H, 8.84.

trans-**3,5-Dimethylcyclohexanone (Va).**—Twenty-eight grams of acid IVa was dissolved in 200 ml. of an aqueous solution of sodium hydroxide, the solution was made just neutral to phenolphthalein with hydrochloric acid, and while stirring the resulting warm solution, 45.4 g. of thorium nitrate tetrahydrate in 100 ml. of warm water was added. The slurry was stirred for an additional hour, and then the thorium salt was filtered and washed well with water. After drying at 100° for several hours the salt weighed 48.7 g. The salt was pyrolyzed in a distilling flask at 30 mm., the volatile products being led in turn through traps cooled in ice and Dry Ice. The pyrolysis began about 300° and the temperature was gradually raised to 450°. The pyrolysis products from both cold traps were washed out with ether, and combined, the ether solution was dried, and the solvent was evaporated. Distillation of the residue with a bath temperature of 125–145° (100 mm.) gave the pure ketone as a colorless liquid, $n^{25}D$ 1.4467, wt. 9.7 g. (52%), reported[10,11] $n^{20}D$ 1.4480, 1.4463. A sample of the ketone was purified by converting it in essentially quantitative yield to the semicarbazone. Recrystallization of the crude material gave plates, m.p. 178.4–179.3°. The melting points reported[10,11] are 193–194° and 186–187°. The mixture melting point with the *cis* isomer (m.p. 200.5–201.5°) was 181–185°.

Anal. Calcd. for $C_9H_{17}ON_3$: C, 58.98; H, 9.35. Found: C, 58.99; H, 9.26.

The dinitrophenylhydrazone, prepared in the usual way, was obtained after two recrystallizations as orange needles, m.p. 109.6–110.3°.

Anal. Calcd. for $C_{14}H_{13}N_4O_4$: C, 54.89; H, 5.92. Found: C, 54.94; H, 5.92.

A sample of pure ketone was recovered from 3.9 g. of the semicarbazone by heating it under reflux with 20 ml. of 3 *N* hydrochloric acid for 1.25 hours. The ketone was extracted with ether, the extracts were washed and dried, and the ether was evaporated. Distillation gave 1.75 g. of ketone, $n^{25}D$ 1.4465.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.66, 75.79; H, 11.23, 10.78.

trans-**3,5-Dimethylcycloheptanone (VIa).**—To a gently stirred mixture of 11.1 g. of ketone Va, 20.4 g. of *p*-tolylsulfonylmethylnitrosamide and 2 ml. of water in 30 ml. of ethanol at 10° there was added dropwise a solution of 2.64 g. of potassium hydroxide in 10 ml. of 50% ethanol during 40 minutes, care being taken not to let the temperature rise above 20°. Stirring was continued for 30 minutes after the addition was complete and then, with external cooling, 10 ml. of cold 6 *N* hydrochloric acid was added to the solution to assure destruction of any unreacted diazomethane. A solution of 5.8 g. of potassium hydroxide in 15 ml. of water was added to the mixture, along with 15 ml. of ethanol, and the mixture was heated under reflux for 30 minutes. The cooled solution was poured into water, and the reaction product was extracted with ether. The ether extracts were washed with water, dried, and the solvent was removed. The residue was then fractionally distilled through a two-foot Podbielniak type column, and the following fractions were collected at 16 mm.: (1) 3.48 g., b.p. 72–74°; (2) 1.15 g., b.p. 74–85°; (3) 0.24 g., b.p. 85–91°; (4) 0.97 g., b.p. 91–91.5°; (5) 1.19 g., b.p. 91.5–92°; (6) 0.10 g., b.p. 92–92.5°; (7) 1.03 g., b.p. 92.5–106°; (8) 0.90 g., b.p. 106–108°. Fractions 4 and 5 were the desired ketone VIa, wt. 2.16 g. (17%), $n^{25}D$ 1.4572, d^{25} 0.9158 g./ml.

Anal. Calcd. for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.01; H, 11.39.

The semicarbazone, obtained in quantitative yield and recrystallized once, had m.p. 164.6–165.5°.

Anal. Calcd. for $C_{10}H_{19}N_3O$: C, 60.88; H, 9.71. Found: C, 61.67, 60.72; H, 9.93, 10.25.

The dinitrophenylhydrazone, prepared in the usual way and once recrystallized, was obtained as orange needles, m.p. 101.7–103.5°.

Anal. Calcd. for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29. Found: C, 56.29; H, 6.14.

Fraction 8 above was presumably a mixture of 3,5- and 4,6-dimethylcycloöctanones in unknown proportions.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.91; H, 11.73. Found: C, 78.11; H, 11.56.

meso-**2,4-Dimethyl-1,5-pentanediol (IIb).**—The *cis*-anhydride Ib was reduced with lithium aluminum hydride in a manner similar to that described for the preparation of IIa. The diol had b.p. 130–132° (5 mm.), $n^{25}D$ 1.4506.

Anal. Calcd. for $C_7H_{16}O_2$: C, 63.59; H, 12.20. Found: C, 63.56; H, 11.88.

meso-β,β′-**Dimethylpimelonitrile (IIIb).**—The diol IIb was converted to the nitrile *via* the iodide as described for the preparation of IIIa. The product had b.p. 131–134°, $n^{25}D$ 1.4463. The yield from IIb was 42%.

Anal. Calcd. for $C_9H_{14}N_2$: C, 71.96; H, 9.39. Found: C, 72.20; H, 9.39.

meso-β,β′-**Dimethylpimelic Acid (IVb).**—Hydrolysis of the nitrile was carried out as described for preparation of the isomer IVa, and recrystallization of the product from benzene–hexane gave the diacid as a colorless crystalline powder, m.p. 95.6–96.8°.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.36; H, 8.75.

cis-**3,5-Dimethylcyclohexanone (Vb).**—Hydrogenation of 3,5-xylenol with Raney nickel at 150° was carried out according to Ungnade and Nightingale.[25] It was found that the reaction went only to about 70% completion in spite of any changes in temperature, pressure and catalyst which were made. Hence the reaction product was taken up in ether, and after removal of the catalyst by filtration, the ether solution was washed well with 10% sodium hydroxide solution to remove unreacted phenol. The alcohol was isolated by distillation, b.p. 75–79° (6 mm.), $n^{25}D$ 1.4531.

The ketone was prepared in 91% yield by oxidizing the alcohol with potassium dichromate following the procedure of Sandborn.[26] Distillation gave the crude ketone, b.p. 57–59° (6 mm.), $n^{25}D$ 1.4412. The pure *cis*-ketone was obtained by converting this material to its semicarbazone and recrystallizing the latter from aqueous ethanol which gave an 85% yield of plates, m.p. 200.5–201.5°. The semicarbazone was hydrolyzed with aqueous ethanolic hydrochloric acid, and the pure *cis*-ketone Vb was obtained by distillation. The recovery was only 66%, apparently because of losses due to volatility. The pure material had $n^{25}D$ 1.4404; reported[10] b.p. 182–183°, $n^{20}D$ 1.4407.

A sample of nitrile IIIb was cyclized by the Thorpe method[27] to give, after hydrolysis and decarboxylation, ketone Vb identical with that obtained from the hydrogenation, $n^{25}D$ 1.4402. The dinitrophenylhydrazone was prepared in the usual way and recrystallized from ethanol–ethyl acetate as orange needles, m.p. 167.3–168.1°.

Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92. Found: C, 54.96; H, 5.89.

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(25) H. E. Ungnade and D. V. Nightingale, THIS JOURNAL, **66**, 1218 (1944).

(26) L. T. Sandborn, "Organic Syntheses," Coll. Vol. I, John Wiley, and Sons, Inc., New York, N. Y., 1948, p. 340.

(27) J. F. Thorpe, *J. Chem. Soc.*, **95**, 1901 (1909).

***cis*-3,5-Dimethylcycloheptanone (VIb).**—The ring expansion of Vb was carried out in an identical manner to that described for the expansion of Va. From 15.0 g. of Vb the following fractions were obtained at 12 mm.: (1) 3.33 g., b.p. 66.5–70.5°; (2) 1.30 g., b.p. 70.5–83.5°; (3) 8.75 g., b.p. 83.5–85.0°; (4) 0.97 g., b.p. 85–94°. Fraction 3 was the desired ketone VIb, $n^{25}\text{D}$ 1.4524, d^{25} 0.9115 g./ml. The semicarbazone, prepared in the usual way and recrystallized once, had m.p. 165.7–166.6°, reported[17] m.p. 166.5°.

Equilibration Studies.—A 100-mg. sample of the ketone to be equilibrated was placed in a small sealed tube with 25 mg. of 10% palladium-on-carbon. The tube, placed in an iron pipe, was heated in a furnace at the desired temperature which was maintained ±3°. The pipe was then removed from the furnace and cooled rapidly by wrapping with a wet towel. The sealed tube was opened to the atmosphere and the catalyst was settled by centrifuging. The liquid was drawn off with a dropper and weighed into a vial and the proper amount of chloroform was weighed in to give the solution for the infrared analysis. The analysis was made in the usual way,[19] and the results are summarized in Table I.

DETROIT, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

The Photolysis and Pyrolysis of Umbellulone[1]

BY JAMES W. WHEELER, JR., AND RICHARD H. EASTMAN

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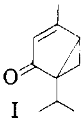
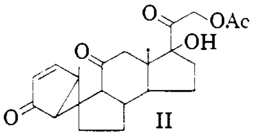
The photolysis of umbellulone produces thymol in essentially quantitative yield, while the pyrolysis of umbellulone produces, in addition to thymol, 5–10% of *sym*-thymol and traces of *p*-cymene.

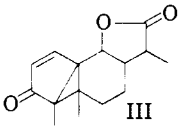
It has recently been found that the cyclohexadienone systems of prednisone acetate and santonin undergo isomerization to the bicyclo[3.1.0]hexenone system found in umbellulone (I) upon ultraviolet irradiation, prednisone acetate yielding II and santonin (III).[2]



I



II



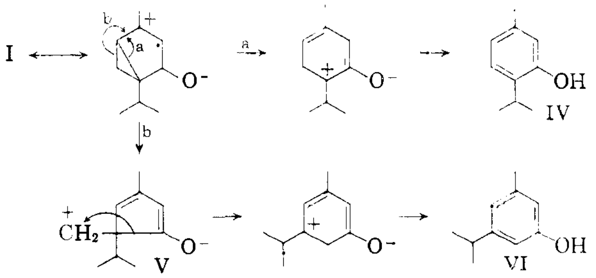
III

We have noted that samples of umbellulone (I) which have been exposed to light invariably contain traces of thymol (IV); and in view of the apparent stability of the umbellulone systems of II and III, it became of interest to determine the course of the photolysis of umbellulone itself.

The photolysis of umbellulone using a variety of sources of radiation (*cf.* Experimental) produces thymol in quantitative yield.

In view of the clear-cut nature of the photolysis, we undertook a reinvestigation of the thermal isomerization of umbellulone, first reported by Semmler[3] to yield thymol, and a vital link in his proof of the structure of umbellulone.[4] Since his observation, the thermal isomerization of umbellulone has continued to be of interest.[5] Contrary to a recent claim,[5c] we have found that the crude pyrolysate from carefully-purified umbellulone contains not only thymol (IV) but also *sym*-thymol (VI) to the extent of 5–10%. and traces of *p*-cymene. Separation of *sym*-thymol from thymol proved difficult, but was achieved by fractional crystallization of the pyrolysate followed by liquid–vapor partition chromatography of the mother liquors. The identity of the *sym*-thymol (m.p. 49.5–50.0°) from the pyrolysis was established by comparison with an authentic sample (m.p. 49.5–50.0°) prepared following the method of Knoevenagel.[6] No depression was observed in a mixed melting point determination, and the two samples had identical infrared absorption spectra.

While the appearance of *sym*-thymol as a pyrolysis product was somewhat surprising,[7] it can be rationalized on the basis of a ring-enlargement in the species V as



It is noteworthy that the pyrolysis and photolysis of umbellulone apparently proceed by different pathways. The results suggest an ionic course for the pyrolysis and a free radical course for the photolysis.

The failure of the umbellulone systems in II and III to undergo facile aromatization on irradiation in analogy to umbellulone may be related to the structural situations in II and III that require the scission of two carbon–carbon bonds for the production of an aromatic system.

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(1) The material of this article is taken from the thesis for the M.S. degree of James W. Wheeler, Jr., at Stanford University.

(2) D. Arigoni, H. Bosshard, H. Bruderer, G. Büchi, O. Jeger and L. J. Krebaum, *Helv. Chim. Acta*, **40**, 1733 (1957); D. H. R. Barton and W. C. Taylor, THIS JOURNAL, **80**, 244 (1958); D. H. R. Barton, P. de Mayo and M. Shafiq, *Proc. Chem. Soc.*, 205 (1957); *J. Chem. Soc.*, 140 (1958).

(3) F. Semmler, *Ber.*, **40**, 5019 (1907); **41**, 3992 (1908).

(4) The recent synthesis of an isomer of umbellulone [H. E. Smith and R. H. Eastman, THIS JOURNAL, **79**, 5500 (1957)] having an ultraviolet absorption spectrum identical with that of umbellulone confirmed the structure proposed by Semmler.

(5) (a) E. K. Nelson, U. S. Patent 1,666,342; (b) W. J. Hund, U. S. Patent 1,967,440; (c) R. S. Aries and M. C. Kidder, "Proceedings of Conference on the Cultivation of Drug and Associated Economic Plants in California," California State Department of Education, 1947, p. 218.

(6) (a) H. E. A. Knoevenagel, *Ann.*, **288**, 325 (1895); (b) *Ber.*, **27**, 2347 (1894).

(7) The possibility that *sym*-thymol arose from an impurity in the umbellulone was considered and is rejected on the basis that gas-chromatographically homogeneous umbellulone was employed, and that thymol was the *only* product of photolysis of the same sample of umbellulone.