[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

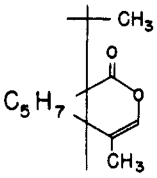
The Degradation of Nepetalactone[1]

BY JERROLD MEINWALD

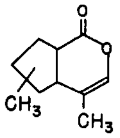
RECEIVED MARCH 29, 1954

Nepetalactone is shown to possess structure IV.

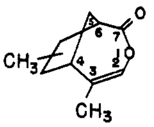
The essential oil obtained from the plant *Nepeta cataria*, of the mint family, is remarkable because of the pronounced attraction it holds for various felids. In a series of dramatic bioassays, McElvain succeeded in demonstrating that the striking physiological activity of this essential oil, best known as Oil of Catnip, was attributable to a single chemical individual, nepetalactone.[2] Pursuing the chemistry of this material, McElvain quickly discerned that nepetalactone was an enol lactone representable by partial structure I, in which the C_5H_7 residue was postulated to form a cyclopentane skeleton.[2-4] Neglecting stereochemical considerations, and assuming the validity of the cyclopentane postulate, it can be readily seen that there are ten discrete structures possible for nepetalactone, five corresponding to formula II and five to formula III. It was the purpose of the present investigation to select the correct structure from this group.



I



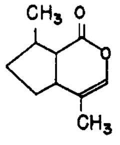
II



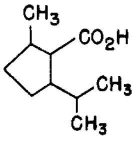
III

Two key observations should serve to cast serious doubt on the likelihood that formulations based on III could be correct. First, the ready thermal regeneration of nepetalactone from its hydrolysis product, the aldehydic acid nepetalic acid,[2] is hard to reconcile with the formation of a seven-membered ring, as III would require. On exactly the same grounds, the conversion of nepetalic acid into a lactol acetate upon treatment with acetic anhydride[2] seems rather surprising. Thus, in spite of the fact that formula III is reasonable in terms of the behavior of McElvain's ultimate degradation product, nepetic acid, it is difficult to reconcile with the properties of nepetalic acid itself. These considerations demand an examination of formula II, in terms of which both the transformations mentioned above would involve closure of a six-membered ring. The cyclizations now become quite reasonable.

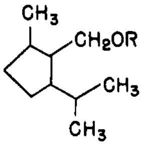
Of the five structures represented by II, that pictured in formula IV appeared to be the most attractive as a working hypothesis, for the reason that it alone comprises two isoprene units joined "head-to-tail." A degradative scheme was devised therefore to test this hypothesis.[5]



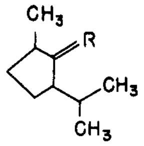
IV



V



VI R = H
VII R = Ac



VIII R = CH₂
IX R = O

Catalytic reduction of nepetalactone resulted in the formation of the expected mixture of hydrogenation and hydrogenolysis products. Dihydronepetalactone, the neutral hydrogenation product, was not fully characterized since it does not form a link in the degradative chain. The acidic fraction, which would correspond to V if the working hypothesis were correct, was purified by distillation. Analytically pure acid was reduced to the alcohol VI with lithium aluminum hydride. Subsequent acetylation gave the ester VII which upon pyrolysis at 530° liberated acetic acid with concomitant olefin formation. Because of experimental difficulties, this olefin (VIII) was not thoroughly purified It was observed, however, that its infrared spectrum was in accord with the proposed structure.[6] Ozonolysis of this olefin gave formaldehyde, identified as its dimedone derivative, and the ketone IX. Identification of this ketone as 2-methyl-5-isopropylcyclopentanone was carried out by a comparison of 2,4-dinitrophenylhydrazones and semicarbazones prepared from the degradation product and from an authentic synthetic sample.[7,8] Infrared spectra

---

[1] A preliminary communication of the results of these investigations has appeared in *Chemistry and Industry*, 448 (1954).

[2] S. M. McElvain, R. D. Bright and P. R. Johnson, THIS JOURNAL, **63**, 1558 (1941); S. M. McElvain, P. M. Walters and R. D. Bright, *ibid*,, **64**, 1828 (1942).

[3] E. J. Eisenbraun, S. M. McElvain and B. F. Aycock, *ibid.*, **76**, 607 (1954).

[4] The possibility that this C_5H_7 residue might be a methylcyclobutane nucleus, not originally considered by McElvain, is superficially attractive because of the fact that β-caryophyllene, which is a second constituent of Oil of Catnip, is known to contain a cyclobutane ring (*Ann. Rep.*, **49**, 180 (1952)). This possibility can be ruled out, however, on the basis of a comparison of the reported properties of the relevant dicarboxylic acids with those of neptic acid, as well as on the basis of some further studies referred to above (reference 3).

[5] It would, of course, be possible to approach the solution of this problem along the already established lines by first determining the structure of nepetic acid. This line of attack, however, suffers from the fundamental intrinsic limitation arising from the circumstance that in the genesis of nepetic acid two unlike groups are *both* converted into carboxylic acid residues. Thus even were the structure of nepetic acid determined directly, there would remain the necessity of deciding between the two modes of attachment of the lactone ring. The present degradative scheme avoids this difficulty by converting one end of the enol lactone ring into a carboxyl and the other into an isopropyl group.

[6] Bands at 3.28, 6.07 and 11.40μ were present, as would be expected for a methylene group exocyclic to a five-membered ring. (For a recent review article on the use of spectra in structure problems, see F. A. Miller in H. Gilman, "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 122.)

[7] J. Golé, *Bull. soc. chim. France*, [5] **16**, 894 (1949).

[8] A second salient feature of this reaction series now becomes apparent. Although ketone IX has two asymmetric centers, and is therefore capable of existing as four stereoisomers, both centers are epimerizable *via* enolization of the carbonyl group. It was therefore anticipated that there should be no stereochemical barrier to carrying out the desired comparison. Further work, aimed at determining the stereochemistry of nepetalactone, is now in progress.

of Nujol mulls of both pairs of derivatives were recorded using a Perkin–Elmer model 21 infrared spectrophotometer. In each case the curves obtained from the natural and synthetic materials were indistinguishable. Direct comparison of the 2,4-dinitrophenylhydrazones by means of melting points and mixture melting points supported the structural assignment. Reasoning back from the structure of ketone IX, it can be seen that the enol lactone IV must represent nepetalactone.

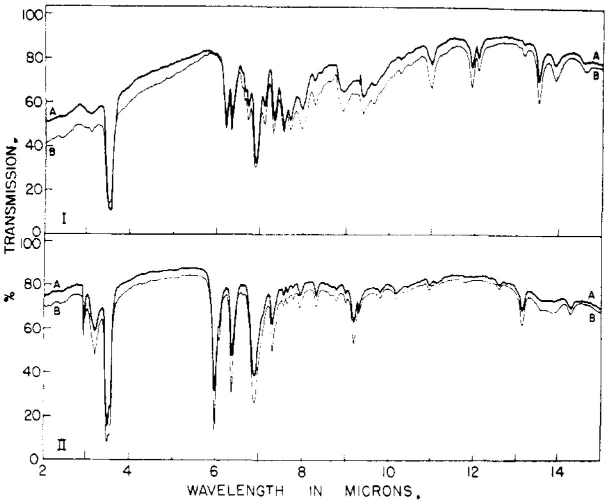


Fig. 1.—Infrared spectra of Nujol mulls of 2-methyl-5-isopropylcyclopentanone derivatives: Curve I, 2-methyl-5-isopropylcyclopentanone 2,4-dinitrophenylhydrazone (A, synthetic; B, natural); Curve II, 2-methyl-5-isopropylcyclopentanone semicarbazone (A, synthetic; B, natural).

Experimental

Nepetalactone (IV).—Oil of catnip was purchased from Fritzsche Bros. The lactone was obtained by distillation as described by McElvain.[2] A fraction of b.p. 129–130° (13 mm.) showed maxima in the double bond region of the infrared at 5.67 and 5.93 μ.

Hydrogenolysis of Nepetalactone.—A solution of 16.6 g. (0.10 mole) of freshly distilled nepetalactone in 50 ml. of glacial acetic acid was shaken in a Parr apparatus with 1.0 g. of Adams platinum dioxide catalyst. The hydrogen uptake stopped at 0.175 mole after several hours. The catalyst was removed by filtration, and most of the acetic acid distilled off under reduced pressure. The residue was then washed thrice with water to remove the remaining acetic acid. The residual oil was taken up in ether and extracted with aqueous sodium carbonate until the aqueous extracts were alkaline. The combined alkaline extracts were acidified with dilute hydrochloric acid, and liberated oily acid V extracted with ether. This ether solution, after washing and drying over anhydrous sodium sulfate, was evaporated to give 11.6 g. of the acid V, b.p. 85° (0.35 mm.), n^{20}_{D} 1.4568.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.59; H, 10.59. Found: C, 70,73; H, 10.40.

Dihydronepetalactone.—The neutral fraction, isolated from the ether layer after the extractions with aqueous sodium carbonate, amounted to 4.2 g. This material distilled mainly at 77–79° (0.30 mm.), and had a single band in the double bond region, corresponding to a simple, saturated lactone (5.79 μ). This substance has not been characterized further.

In a series of hydrogenolysis experiments, the ratio of acidic to lactonic product varied. The results described above are those obtained in a typical run.

Lithium Aluminum Hydride Reduction of V.—A suspension of 5 g. of lithium aluminum hydride (0.53 eq. of $H^{\ominus}$) in 100 ml. of dry ether was stirred vigorously while 6 g. of V in 20 ml. of dry ether was added dropwise. Stirring was continued for five hours at room temperature, after which a saturated aqueous solution of sodium sulfate was added slowly to decompose the complex and excess reagent. The ether layer was separated, and the aqueous phase extracted twice with small portions of ether. The combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent left 5.3 g. of the alcohol VI, b.p. 60° (0.70 mm.), n^{20}_{D} 1.4621. The infrared spectrum showed a strong maximum at 3.0 μ, as expected for an alcohol.

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.95; H, 12.82. Found: C, 76.90; H, 12.89.

Acetylation of VI.—A mixture of 15.7 g. of VI, 12.4 g. of acetic anhydride and 9.6 g. of dry pyridine was allowed to stand overnight at room temperature. The product was worked up in standard fashion by pouring into ice-water, extracting the product with ether, and washing the ether layer repeatedly with dilute hydrochloric acid and water. In this way 17.9 g. of acetate VII, b.p. 53° (0.40 mm.), n^{20}_{D} 1.4467, was obtained (infrared max. 5.76 μ).

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.72; H, 11.00.

Pyrolysis of VII.—A glass column (*ca.* 30 × 3 cm.), packed with carborundum chips, was heated to 500° and slowly swept with dry nitrogen. A solution of 5.7 g. of VII in 10 ml. of *n*-pentane was dropped through the tube at the rate of 20 drops per minute, and the pyrolysis products collected in a Dry Ice trap. In this way a yellow liquid with the characteristic odor of acetic acid was obtained. Washing the product with base to remove the acetic acid and removal of the pentane by distillation gave 4.2 g. of a residue. Infrared examination of this crude product showed it to consist chiefly of unchanged acetate VII, plus a small amount of an olefin (new $\lambda_{max.}$ at 3.28, 6.07 and 11.40 μ). Fractionation of this material either at atmospheric or reduced pressure was prevented by excessive foaming.

In a second attempt, 17.9 g. of acetate VII was pyrolyzed without diluent at 510°. Working up as described above gave 11 g. of neutral material which was again shown to be a mixture of ester and olefin by infrared analysis. This mixture was submitted to pyrolysis at 530° to give 7 g. of neutral product. Distillation of this substance was once more made difficult by an irrepressible tendency to foam. It was possible, however, to isolate 3 g. of a pale yellow oil (VIII), b.p. 84–90° (150 mm.), which decolorized bromine in carbon tetrachloride and potassium permanganate solution. This fraction was free of acetate bands, and showed $\lambda_{max.}$ at 3.28, 6.07 and 11.40 μ.

Ozonolysis of VIII.—A methylene chloride solution of 2.8 g. of the crude olefin VIII was treated with excess ozone at −78°. The solution of ozonide was reduced by pouring it into a suspension of 8 g. of zinc dust in 25 ml. of glacial acetic acid. The mixture was stirred at room temperature for four hours, and refluxed for one additional hour. At this point the methylene chloride and formaldehyde were distilled into a flask containing 4.3 g. of dimedone, 30 ml. of 75% ethanol and a few drops of piperidine. Concentration of the distillate to a total volume of 20 ml. resulted in the separation of 1.25 g. (23%) of the dimedone derivative of formaldehyde, m.p. 189–190°.

The acetic acid solution was poured into water and extracted with ether to give 2.5 g. of crude ketone as a mobile yellow liquid. Distillation of 2.2 g. of this crude ketone, still plagued by foaming, gave 1 g. of product (IX), b.p. 181–186° (740 mm.). This material showed an intense $\lambda_{max.}$ at 5.78 μ. It was converted into both a semicarbazone and 2,4-dinitrophenylhydrazone. After several recrystallizations, these were compared with the same derivatives prepared from an authentic sample of 2-methyl-5-isopropylcyclopentanone, synthesized according to Golé.[7] Comparison of 2,4-dinitrophenylhydrazones: natural, m.p. 169–171.5°; synthetic, m.p. 170–171.5°; mixture, m.p. 169–171.5°.

2-Methyl-5-isopropylidenecyclopentanone 2,4-dinitrophenylhydrazone: *Anal.* Calcd. for $C_{15}H_{18}O_4N_4$: C, 56.60; H, 5.66; N, 17.61. Found: C, 56.81; H, 5.78; N, 17.39.

2-Methyl-5-isopropylcyclopentanone 2,4-dinitrophenylhydrazone: *Anal.* Calcd. for $C_{15}H_{20}O_4N_4$: C, 56.26; H, 6.25; N, 17.50. Found: C, 56.25; H, 6.34; N, 17.55.

Acknowledgment.—The author wishes to express his appreciation to Miss Yun-Wen Chu for valuable aid with the experimental work. Support of this research in its initial stages was generously provided by the du Pont Company. Microanalyses were performed by Mrs. M. Libowitz, and the Geller Laboratories, Hackensack, N. J.

ITHACA, NEW YORK

[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

The Diels–Alder Reaction and the Rearrangement of the Maleic Anhydride Adducts of 6,6-Dimethylfulvene

BY DAVID CRAIG, J. J. SHIPMAN, JACK KIEHL, FRANZ WIDMER, RAY FOWLER AND A. HAWTHORNE

RECEIVED MARCH 2, 1954

For short periods of reaction between room temperature and 80° it was found that 6,6-dimethylfulvene and maleic anhydride react almost completely to form mixtures containing about equal amounts of the previously studied *endo* and *exo* adducts. These rearrange so that during a few hours in concentrated benzene solution at 80°, an equilibrium mixture containing 85 to 88% of the *exo* isomer is obtained. Both adducts undergo retrogression, the *endo* the more readily. Retrogression does not seem necessary for rearrangement. This particular diene synthesis is one in which Alder rule II does not apply, *i.e.*, the reaction is not stereospecific for the reason that an Alder complex is unlikely. An infrared spectrophotometric technique for determining the ratio of *endo* to *exo* adduct in solid mixtures is described.

Retrogression in the Diels–Alder reaction in some instances has been held to account for the rearrangement of an initially formed, though more unstable, isomer. Alder and Trimborn[1,2] postulate that this dissociation–recombination mechanism, first reported on in some detail by Woodward and Baer[3] is a general one. A different view recently has been published for the case of the cyclopentadiene–maleic anhydride adducts,[4] for which evidence was presented to show that the adducts rearranged into each other without intermediate dissociation. This "direct" mechanism involved a non-isolable intermediate and hydrogen migration. The present paper describes the application of a direct mechanism to an *endo–exo* rearrangement in the fulvene series in which a hydrogen shift seems unlikely and in which dissociation is easily recognized.

Alder and Rührmann[5] reported 60 to 70% conversion to mixtures of the *endo* adduct (I) and *exo* adduct (II) when 6,6-dimethylfulvene and maleic anhydride are contacted between 0 and 80° in ether or benzene. They also reported the yield of II to be strongly favored at the expense of I by temperature increase. II was found to dissociate less readily than I.

We have found that the melting points of I and II are somewhat higher than those previously reported and are 118 and 140°, respectively. Also in concentrated solution the reaction appears to be essentially complete during 16 hours at 25° and at least 94% complete during five minutes at 80°. The ratio of II to I was 1.1 at 15° and 1.3 at 80°; however, when the reaction was conducted for a period of three hours at 80° or when the *endo* adduct was refluxed in benzene for this period, an 85% yield of II was secured. When II was heated for five hours at 80° in benzene, infrared spectrophotometric analysis of the product indicated that a 12% conversion to the *endo* adduct had resulted. We infer therefore (a) that the equilibrium mixture contains between 85 and 88% of II and (b) that Alder and Rührmann's yield of II at 80° is the result of initial *exo* adduct formation combined with rearrangement of initially formed I. This was confirmed when it was found that I during a period of five minutes in benzene at 80° gave 97% of a product containing only about 11% of II, *i.e.*, most of the II isolated from the diene synthesis conducted at 80° for five minutes must have been formed as an initial product. Alder and Rührmann's picture appears confused because of the possibility that their product melting at 112° was not pure and may have contained II. We have found that maleic anhydride does not affect the rearrangement but that it represses dissociation into fulvene and maleic anhydride, both of which were isolated as dissociation products.

It is of interest to attempt the fitting of the behavior of I and II, as well as the unusual structure of the fulvene, into the general background of the diene synthesis, especially that having to do with Alder rule II.[6] One is tempted to consider the adducts to be formed through Alder complexes Ia and IIa. These are the complexes which would result if the fulvene were a normal diene. However, considering the resonance forms of 6,6-dimethylfulvene, a more probable complex would be a hybrid in which IIb would make a major contribution and IIa a minor one. An *endo* type similar to IIb obviously does not need to be considered. Since nearly half of the product is I, this line of reasoning fails and a mechanism not involving an Alder complex is needed to account for the formation of I as well as II.

If charged forms really make great contributions to the hybrid of the fulvene, as is indicated by its high dipole moment,[7] then I and II should be

---

[1] K. Alder and W. Trimborn, *Ann.*, **566**, 58 (1950).

[2] Compare J. A. Berson and R. Swidler, THIS JOURNAL, **75**, 1721 (1953).

[3] R. B. Woodward and H. Baer, *ibid.*, **66**, 646 (1944).

[4] D. Craig, *ibid.*, **73**, 4889 (1951).

[5] K. Alder and R. Rührmann, *Ann.*, **566**, 1 (1950).

[6] Alder rule III has recently been proposed. It states in effect that the diene always reacts in the *cisoid* configuration (*cf.* K. Alder, *Ann.*, **571**, 157 (1951)). This principle has long been recognized; thus in the case where the *cisoid* configuration is impossible, reaction either fails or takes place with difficulty. Examples are 2,3-dichloro-1,3-butadiene (G. J. Berchet and W. H. Carothers, THIS JOURNAL, **55**, 2006 (1933)), *cis*-1-phenylbutadiene (O. Grummit and F. J. Christoph, *ibid.*, **73**, 3479 (1951)), 2,3-di-*t*-butyl-1,3-butadiene (H. J. Backer, *Rec. trav. chim.*, **58**, 643 (1939)) and *cis*-piperylene (D. Craig, THIS JOURNAL, **65**, 1006 (1943); **72**, 1678 (1950)). Adduct I and II, of course, have structures in accord with rules I and III.

[7] G. W. Wheland and D. E. Mann, *J. Chem. Phys.*, **17**, 264 (1949).