366 mg. of Ic, m.p. 132–133°. Reworking of the mother liquors increased the yield of Ic to 536 mg. (54%).

Ia from Id.—A mixture of 202 mg. of the *trans-trans*-acid Id, 7 ml. of acetic anhydride and 1 mg. of sodium acetate was refluxed for 16 hours. Then the mixture was slowly fractionated through a 15-inch Podbielniak column until the boiling point rose to 138° (1 hour). The remainder of the acetic anhydride was removed below 70° (10 mm.). The residual oil was transferred to a centrifuge tube, made basic with a saturated solution of barium hydroxide, chilled centrifuged, and decanted. The precipitated barium salt was washed with ether to remove any soluble organic material and then the acid was isolated from the salt in the usual way. The resulting acid crystallized slowly. In one run it was recrystallized from ether–petroleum ether, giving a 4% yield of *cis-trans*-acid Ia, m.p. 110–112°, mixed m.p. with a pure sample of Ia, 111–115°. In another run the crude acid from the precipitated barium salt was converted to its anhydride and the anhydride mixture evaporatively distilled. From a quantitative infrared analysis this anhydride mixture was calculated to contain 63% of the *cis-trans*-anhydride Xa and 37% of the *cis-cis*-anhydride Xb.

3-Methylcyclopentane-1,2-dicarboxylic Acid (I) Prepared by the Procedure of Blomquist, *et al.*—A sample of this sublimed and recrystallized acid (I),[12] m.p. 111–114°, gave no precipitate with barium hydroxide. A second sample was recrystallized seven times from acetonitrile, giving a 2% yield of Ic, m.p. 133–134°, m.p. undepressed by admixture with an authentic sample of Ic. Attempts to isolate Id from the mother liquors were without success.

A third sample was converted to the dimethyl esters, $n^{25}\text{D}$ 1.4468 after two evaporative distillations. Assuming this ester mixture to contain only the esters of Ic and Id, it was calculated from this refractive index to consist of 47% of the former and 53% of the latter ester. By the previously described treatment with sodium methoxide, this ester mixture was converted to the same (refractive index, infrared spectrum) equilibrated ester mixture as had been obtained from the esters of the acids Ia–d.

MADISON 6, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

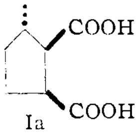
The Configurations of the Nepetalactones and Related Compounds

BY ROBERT B. BATES,[1] E. J. EISENBRAUN[2] AND S. M. MCELVAIN

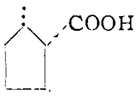
RECEIVED JANUARY 25, 1958

The nepetalactone fraction as obtained from oil of catnip is shown to consist of two stereoisomeric lactones. The predominant one has the *cis-trans* configuration IXa and the one present in lesser amounts has the *trans-cis* configuration IXc. The lactone with the *cis-trans* configuration is shown to be the precursor of the *trans-trans*-nepetonic acid (IId) which yields the *trans-trans*-nepetic acid (Id) on oxidation. From the *trans-cis*-nepetalactone, *trans-cis*-nepetonic acid (IIc) and *trans-cis*-nepetic acid (Ic) have been obtained. These results require revision of the previously assigned configurations of the nepetalinic acids to those shown in Xa–d and of the ant lactones, iridomyrmecin and isoiridomyrmecin, to XIIa and b.

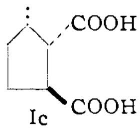
In the previous paper[3] it was shown that the *trans*-nepetic acid obtained from the degradation of nepetalactone *via* nepetalic and nepetonic acids has the *trans-trans* configuration Id rather than the previously assigned[4] *trans-cis* configuration Ic, and that the *cis*-nepetic acid had been correctly assigned[4] the *cis-trans* structure Ia. Although the anhydrides obtained[3] from both *trans*-nepetic acid and *dl-trans-trans*-3-methylcyclopentane-1,2-dicarboxylic acid (Id) were mixtures (infrared spectra) of the anhydrides of the two *cis*-acids, represented as the enantiomers Ia and Ib, only the *cis-trans*-acid Ia could be isolated from these anhydride mixtures.



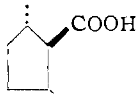
Ia



Ib

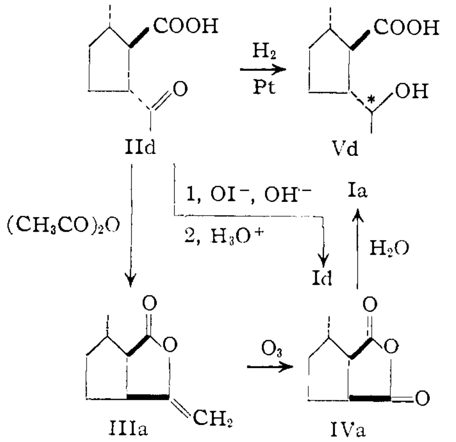


Ic



Id

It appears that nepetonic acid, the immediate precursor of Id, must also have the *trans-trans* configuration IId, instead of the previously assigned[4] *trans-cis*[5] configuration, because it yields Id *via* the haloform reaction and is converted by hydrogenation to a nepetolic acid Vd, m.p. 105°, whose failure to lactonize indicates the *trans* relationship between the functional substituents. Also, the transformation of nepetonic acid to nepetonolactone IIIa, the configuration of which has been established by its conversion *via* the anhydride IVa to *cis*-nepetic acid (Ia), is better explained by the *trans-trans* configuration IId because epimerization at the α-position to the carbonyl function should be more facile than epimerization at the α-position to the carboxyl group, which would be required if nepetonic acid had the *trans-cis* configuration. Consequently, nepetonic acid (IId) and the various compounds that have been prepared from it now are assigned the configurations:



With these configurations established for nepetonic acid and its derivatives, it is apparent that

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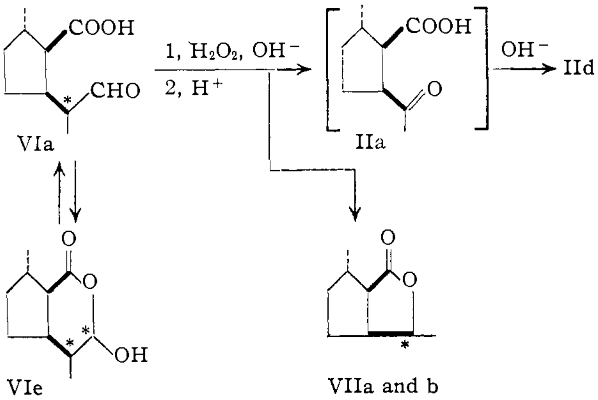
(3) R. B. Bates, E. J. Eisenbraun and S. M. McElvain, THIS JOURNAL, **80**, 3413 (1958).

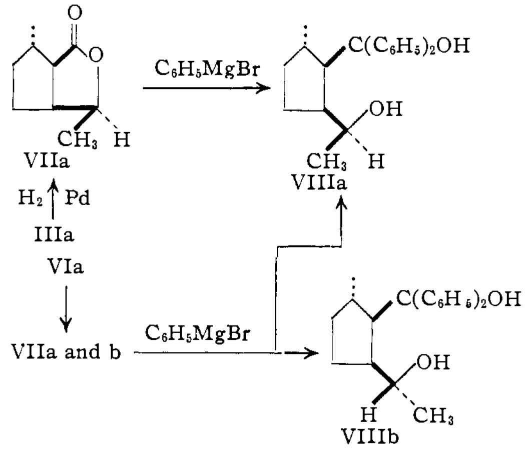
(4) S. M. McElvain and E. J. Eisenbraun, *ibid.*, **77**, 1599 (1955).

(5) In this and all other designations of configurations in this paper the relationship of the functional substituents is given first and that of the methyl group and the adjacent functional substituent second.

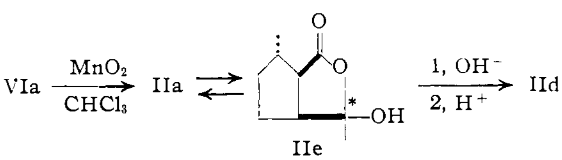
the *trans-cis* configuration previously assigned[4] to nepetalic acid, the immediate precursor of nepetonic acid IId, requires revision. Nepetalic acid, as it is obtained by hydrolysis of nepetalactone from oil of catnip, is an oily mixture from which a crystalline stereoisomer, m.p. 73–75°, slowly separates and may be isolated in about 30% yield.[4] This crystalline acid, whose infrared spectrum indicates that it exists as the lactol form VIe, gives both nepetonic acid (IId) and the nepetolactones (VIIa and b) on oxidation with alkaline hydrogen peroxide. While *trans-trans*-nepetalic acid could give IId, it is difficult to see how the lactones VIIa and b would result from a nepetalic acid of this configuration. The *trans-cis* configuration, previously assigned[4] to nepetalic acid, would not be expected to yield IId as this transformation would involve isomerization of the initially formed *trans-cis*-nepetonic at the asymmetric center carrying the acetyl substituent, and also at the α-position to a carboxylate anion; the latter change seems quite unlikely. The only structure that can reasonably account for the formation of *trans-trans*-nepetonic acid (IId) and the *cis-trans*-lactones VIIa and b is *cis-trans*-nepetalic acid (VIa). Oxidation of VIa gives initially *cis-trans*-nepetonic acid (IIa), which in the alkaline medium epimerizes at the center holding the ketonic function to the *trans-trans* structure IId. A competing oxidation process simultaneously converts VIa to the nepetolactones VIIa and b, which are not susceptible to epimerization and, consequently, retain the same configuration as their precursor VIa.



Since the structure of nepetonolactone (IIIa), was well established by its conversion *via* IVa to Ia, it seemed desirable to reduce IIIa to the saturated lactone and establish the identity of the product with the nepetolactones obtained from the oxidation of nepetalic acid (VIa) with alkaline hydrogen peroxide. Hydrogenation of IIIa gave a 58% yield of a lactone whose infrared spectrum was quite similar to that of the lactone epimers VIIa and b; the essential difference was that the peaks in the 7–10 μ region of the spectrum of the new lactone were much better defined. The saturated lactone from IIIa was converted with phenylmagnesium bromide to a solid glycol by the procedure that had been used[4] to convert VIIa and b to a mixture of glycols, VIIIa and b, from which each pure glycol was separated in about 10% yield. The lactone derived from IIIa gave a 29% yield of a glycol, m.p. 155–156°, which was identical (mixed m.p., infrared spectrum) with one of the glycols, m.p. 156–157.5°, obtained from VIIa and b. Assuming that hydrogen addition was predominantly to the less hindered side of IIIa in the hydrogenation, the new lactone is mainly VIIa and the glycol, m.p. 155–156°, is VIIIa; the other glycol, m.p. 141–143°, from the nepetolactones VIIa and b then has the configuration VIIIb. This relationship of IIIa to VIIa and b excludes the *cis-cis* structure for the latter compounds.



Further evidence for the configuration VIa for crystalline nepetalic acid was obtained from its oxidation with manganese dioxide in chloroform solution.[6] The product of this oxidation was an oil whose infrared spectrum showed bands at 2.9 and 5.67 μ indicative of the hydroxyl and the γ-lactol carbonyl groups of the lactol IIe of *cis*-nepetonic acid (IIa). The formation of such a lactol obviously requires that the functional substituents of this nepetonic acid have a *cis* arrangement. This acid gave a yellow-orange, alkali-soluble, 2,4-dinitrophenylhydrazone, which could not be obtained crystalline. However, when the acid IIa was warmed in alkaline solution, it was transformed into an acid which had an infrared spectrum and gave a 2,4-dinitrophenylhydrazone that were identical with the spectrum and 2,4-dinitrophenylhydrazone of *trans*-nepetonic acid (IId) that had been obtained by the oxidation of VIa with alkaline hydrogen peroxide.



If the crystalline nepetalic acid, m.p. 73–75°, has, as the above evidence indicates, the configuration at the cyclopentane nucleus shown in VIa ⇄ VIe, then the nepetalactone which yields this acid on hydrolysis must have the configuration IXa. Hydrolysis of this lactone and oxidation of the re-

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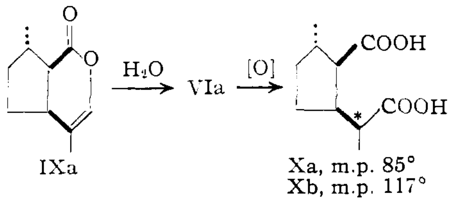
[6] (a) The authors are indebted to Dr. R. J. Highet who first carried out this oxidation of nepetalic acid (*cf.* R. J. Highet and W. C. Wildman, THIS JOURNAL, **77**, 4399 (1955)); (b) the manganese dioxide, prepared according to the method of Attenburrow, *J. Chem. Soc.*, 1094 (1952), was generously donated by Dr. R. J. Highet.

sulting nepetalic acids should produce two nepetalinic acids (Xa and b) epimeric at the asymmetric center (indicated by asterisk). These acids are readily separated by virtue of the fact that one of them, m.p. 85°, which is obtained in practically quantitative yield from the oxidation of nepetalic acid, m.p. 73–75°, forms an insoluble barium salt. The epimer of this acid melts at 117°.



IXa

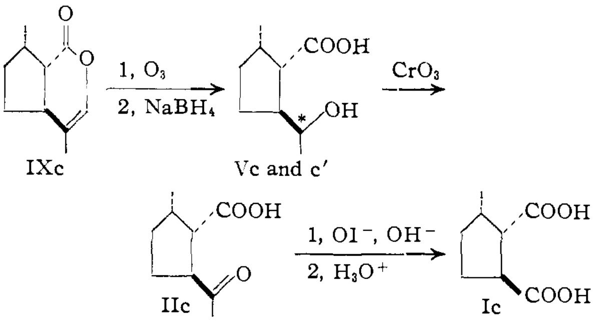
Xa, m.p. 85°
Xb, m.p. 117°

When the nepetalic acids resulting from the hydrolysis of nepetalactone, as obtained directly from the oil by low pressure distillation, were oxidized only a 20% yield of the nepetalinic acid, m.p. 85°, could be separated *via* its insoluble barium salt. The acidic material recovered from the soluble barium salts was an oil that could not be induced to crystallize. These results indicate that the natural nepetalactone is not the single compound IXa but contains a stereoisomer that yields sufficient of the other nepetalinic acids to prevent crystallization of the stereoisomer Xb.

Attempts were made to separate these nepetalactones by vapor chromatography, but the results were inconclusive because of the high boiling point (*ca.* 250°) nepetalactone; it was eluted from the column only as a broad peak under the conditions used.

A new degradation of nepetalactone established the presence of two stereoisomers. When the nepetalactone, as obtained from oil of catnip, was treated in methanol solution containing pyridine with ozone and the resulting solution then treated with a large excess of sodium borohydride, several products were obtained. The main products, isolated in 51% yield, were the epimeric nepetolactones VIIa and b derived from IXa; in addition to this material a 26% yield of a mixture of nepetolic acids (V), m.p. 93–100°, was obtained. Most of the remaining material (16% of the weight of the nepetalactone) was a neutral, non-lactonic fraction, which was not investigated further.

Recrystallization of the acidic fraction gave a new nepetolic acid (Vc or c′), m.p. 139–140°, amounting to 21% of the crude acidic material. This new acid was oxidized with chromic acid and the resulting nepetonic acid converted to a 2,4-dinitrophenylhydrazone, m.p. 171–172° (82% yield from the nepetolic acid). This derivative was different (mixed m.p.) from the 2,4-dinitrophenylhydrazone (m.p. 174–175°) of *trans-trans*-nepetonic acid (IId). Consequently, the nepetolic acid, m.p. 140°, has the *trans-cis* configuration and is one of the epimeric pair Vc and c′. It follows, therefore, that the *trans-cis*-nepetalactone (IXc) was the precursor of this new nepetolic acid, and the nepetonic acid (IIc) which the latter compound gave on oxidation. This conclusion was confirmed by the conversion of IIc in 47% yield to *trans-cis*-nepetic acid (Ic), m.p. 114–115°, whose dimethyl ester has an infrared spectrum indistinguishable from the spectrum of *dl-trans-cis*-dimethyl 3-methylcyclopentane-1,2-dicarboxylate.[3]



IXc

Vc and c′

IIc

Ic

The crude acidic fraction, m.p. 93–100°, from the borohydride reduction was converted *via* the same oxidation sequence to the 2,4-dinitrophenylhydrazone of IIc in 73% yield and into the nepetic acid Ic in 48% yield. Since the yields of Ic and IIc from this crude acidic fraction and from the pure nepetolic acid, m.p. 139–140°, are comparable, it would appear that there is little, if any, of the *trans-trans*-nepetalactone present in the oil of catnip; otherwise the acidic fraction from the borohydride reduction would have been contaminated with the *trans-trans*-nepetolic acids, one of which, Vd, has been prepared by the hydrogenation of *trans-trans*-nepetonic acid (IId).

The isolation of the nepetolactones VIIa and b in 51% yield in this ozonolysis experiment shows that *cis-trans*-nepetalactone (IXa) is the main constituent of the nepetalactone fraction. From the yield of the nepetolic acids Vc and c′, it may be concluded that at least 26% of *trans-cis*-nepetalactone (IXc) is also present.

The revisions of the configurations of the nepetalactones and their degradation products, which the work reported above necessitates, is of particular significance in regard to the stereochemistry of a group of compounds recently isolated from ants.[7] Iridomyrmecin (XIIb) has been related by oxidation to the nepetalinic acid Xb, m.p. 117°, and isoiridomyrmecin (iridolactone) (XIIa), an epimer of iridomyrmecin at the asymmetric center (asterisk), has been similarly related to the nepetalinic acid Xa, m.p. 85°. Recently a half-ester XI of Xa has been converted by lithium aluminum hydride reduction to isoiridomyrmecin,[8] thus demonstrating the interconvertibility of the ant lactones and compounds derived from nepetalactone. Since the *trans-cis* configuration, originally assigned to the ring substituents of these nepetalinic acids, has been used for the ant lactones[7] it now becomes necessary to revise the configuration of these lactones to XIIa and b in order for them to conform with the configurations of their oxidation products Xa and b. It is also necessary to revise the configuration of the nepetalinic acids, m.p. 111° and 115°, which were obtained, respectively, from epimerizations of the dimethyl ester of Xa and of

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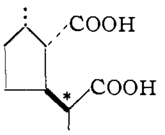
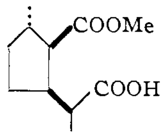
[7] M. Pavan, *Chim. e industria* (*Milan*), **37**, 714 (1955); R. Fusco, R. Trave and A. Vercellone, *ibid.*, **37**, 251, 958 (1955); G. W. K. Cavill, *et al.*, *Chemistry & Industry*, 351 (1953); 465 (1956); *Austral. J. Chem.*, **9**, 288 (1956).

[8] E. J. Eisenbraun and S. M. McElvain, *J. Org. Chem.*, **22**, 976 (1957).

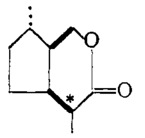
the half-ester XI[4] to the *trans-cis* configuration Xc and d.



Xc, m.p. 111°
Xd, m.p. 115°



XI



iridomyrmecin XIIb
isoiridomyrmecin XIIa

The *cis-trans* structure Xa for the nepetalinic acid that melts at 85° better explains the pyrolysis behavior of this acid than does the previously assigned[4] *trans-cis* structure. The anhydride formed by the pyrolysis of nepetalinic acid, m.p. 85°, gave back 58% of this acid on hydrolysis.[4] The preponderance of this *cis*-anhydride in the pyrolytic anhydride mixture parallels the yield of *cis*-anhydride from pyrolysis of *cis*- or *trans*-2-carboxycyclopentaneacetic acid. Either of these acids at 240° produced an equilibrium mixture that contained 86% of the *cis*-anhydride.[9]

Experimental

Reduction of Nepetonolactone (IIIa) to the Nepetolactones VIIa and b.—A mixture of 162 mg. of IIIa,[4] $n^{25}\mathrm{D}$ 1.4796, 5 ml. of ethyl acetate and 20 mg. of 6% palladium-on-barium sulfate was stirred under a hydrogen atmosphere. After 24 hours, absorption of hydrogen had ceased at 68% of the theoretical amount. The catalyst was filtered off, washed with ethyl acetate, and the ethyl acetate removed by evaporation on a steam-bath. Then 3 ml. of 10% sodium hydroxide solution was added and the mixture heated on a steam-bath for half an hour, cooled, washed with ether, acidified with 6 *N* hydrochloric acid, and extracted with ether. The ether solution was washed with saturated sodium bicarbonate solution to remove acidic material, the ether evaporated, and the residual lactone evaporatively distilled at 75° (0.1 mm.), to yield 95 mg. (58%) of nepetolactone (VIIa and possibly some VIIb), $n^{25}\mathrm{D}$ 1.4652. The infrared spectrum of this lactone was quite similar to that of the nepetolactones VIIa and b obtained from the alkaline hydrogen peroxide oxidation of nepetalic acid[4] (VIa); the only significant difference was that the peaks in the 7–10 μ region of the new lactone were better defined.

A sample of this lactonic hydrogenation product gave a 29% yield of the glycol VIIIa, m.p. 155–156°, on treatment with phenylmagnesium bromide. In a mixed melting point determination this glycol did not depress the melting point of the 156–157.5° glycol prepared[4] from nepetolactones resulting from the alkaline hydrogen peroxide oxidation of nepetalic acid (VIa); the infrared spectra of these two glycol samples were superimposable.

Oxidation of Nepetalic Acid (VIa) to *cis*-Nepetonic Acid (IIa) with Manganese Dioxide.—A mixture of 2.95 g. of nepetalic acid (VIa), m.p. 73–75°, $[\alpha]^{28}\mathrm{D}$ +46.8° (*c* 1.16 in chloroform), 100 ml. of chloroform and 16.1 g. of manganese dioxide[8b] in a 250-ml. erlenmeyer flask was stirred with a Teflon covered magnetic stirring bar for 130 hours at room temperature. At the beginning of the reaction the infrared spectrum of nepetalic acid in chloroform showed a strong carbonyl band at 5.78 μ and a hydroxyl band at 3.00 μ (lactol form VIe). As the oxidation progressed the carbonyl band gradually shifted to 5.64 μ while the hydroxyl band diminished in size and shifted to 2.8–2.9 μ.[10]

The reaction mixture was filtered through a sintered glass funnel containing a layer of magnesium sulfate. The filter cake was washed with several portions of chloroform and the filtrate concentrated under diminished pressure to leave 1.23 g. (45%) of crude IIc. A portion of this oily product was distilled at 85° (0.1 mm.) with considerable decomposition to give a colorless oil, which showed the presence of a carbonyl band at 5.67 μ and a hydroxyl band at 2.8–2.9 μ in the infrared spectrum.

A second portion of the crude oil was treated with Brady reagent[11a]; a yellow-orange, alkali-soluble,[11b] precipitate formed but this material failed to crystallize even after chromatography on silica gel.

A third portion of the oil was dissolved in 10% sodium hydroxide solution and the resulting yellow solution was heated on the steam-bath for 1 hour, cooled, acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated to a pale yellow oil which was evaporatively distilled at 120° (0.2 mm.). The infrared spectrum of the resulting colorless oil (in chloroform) showed no hydroxyl band, but had instead a typical absorption of the carboxyl group in the region of 2.9–4.2 μ; it also had a single strong carbonyl band at 5.80 μ. This spectrum was identical to that of *trans*-nepetonic acid (IId) previously prepared from nepetalic acid by oxidation with alkaline hydrogen peroxide.[4] The *trans*-nepetonic acid (IId) prepared by alkali epimerization of IIc was treated with Brady reagent.[11a] In this case the derivative formed immediately as alkali-soluble,[11] canary-yellow needles which upon a single recrystallization from aqueous ethanol melted at 170–172°. These needles showed no depression in melting point on admixture with an authentic specimen of the 2,4-dinitrophenylhydrazone of IId. The infrared spectra, in chloroform, of these two 2,4-dinitrophenylhydrazones were identical.

Conversion of Nepetalactone to Nepetalinic Acids.—The procedure below was patterned after the conversion of crystalline nepetalic acid (VIa) to the nepetalinic acid half-ester XI.[4] It was demonstrated first that this half-ester was saponified to the 85° nepetalinic acid (Xa) with less than 4% epimerization to other isomers by the procedure used below.

A mixture of 204 mg. of nepetalactone[12] as obtained directly from oil of catnip by distillation under diminished pressure,[13] $n^{25}\mathrm{D}$ 1.4878, and 30 ml. of 0.046 *N* sodium hydroxide solution was stirred at room temperature for 2 hours. The basic solution was extracted with ether to remove 5.0 mg. of non-lactonic neutral material. The aqueous solution was acidified with 6 *N* hydrochloric acid, saturated with sodium chloride, and extracted with ether. The ether solution was dried over magnesium sulfate for 1 hour, filtered, and treated with an ethereal solution of distilled diazomethane until the green color persisted for a few seconds. The green color was dispelled with a drop of acetic acid and the ethereal solution was dried over potassium carbonate. After filtering, the ether was evaporated. A slow stream of dry air was blown over the residual aldehydoester for a week.

The resulting oil was taken up in ether and the ethereal solution extracted with saturated sodium bicarbonate solution. The ether solution yielded 25 mg. of neutral material, which was discarded. The bicarbonate solution was acidified with 6 *N* hydrochloric acid and extracted with ether. Evaporation of the ether gave 150 mg. (59%) of nepetalinic acid half-ester.

This half-ester was heated on a steam-bath in a centrifuge tube with 0.5 ml. of 0.54 *N* barium hydroxide solution for 16 hours. After cooling, centrifuging and decanting, the precipitated barium salt was washed with 1 ml. of water. The insoluble barium salt yielded 24 mg. (17%) of nepetalinic acid Xa, m.p. 79–82°. The soluble barium salt gave 116 mg. of oil, which was chromatographed on silicic acid, removing some monobasic acid from the nepetalinic acid. The dibasic acid fraction (77 mg., 55%) still failed to crystallize. Its infrared spectrum in chloroform solution was similar to the spectra of the previously prepared[4] nepetalinic acids.

Ozonization of Nepetalactone and Reduction of Product with Sodium Borohydride. *trans-cis*-Nepetolic Acid (Vc).—

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[9] A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 956 (1934).

[10] *Cf.* K. Tsuda, K. Tanabe, I. Iwai and K. Funakoski, THIS JOURNAL, **79**, 5721 (1957), for similar carbonyl and hydroxyl group absorption in the infrared.

[11] (a) O. L. Brady, *J. Chem. Soc.*, 756 (1931); (b) the derivative readily dissolves in dilute aqueous alkali to give a deep burgundy color characteristic of alkaline solutions of 2,4-dinitrophenylhydrazones of keto acids.

[12] The authors are indebted to Professor J. Meinwald, Department of Chemistry, Cornell University, for a generous gift of nepetalactone.

[13] S. M. McElvain, R. D. Bright and P. R. Johnson, THIS JOURNAL, **63**, 1558 (1941).

A 3.0-g. sample of nepetalactone, $n^{25}D$ 1.4878, was added to a mixture of 150 ml. of methanol and 3 ml. of pyridine which had been chilled to −70°. Ozone was passed in through a fritted glass bubbler until the blue end-point was observed (23 min.). A solution of 1.5 g. of sodium borohydride in 15 ml. of water was then added. After half an hour at −70°, a similar portion of sodium borohydride solution was added and the temperature was allowed to rise to 0°. Similar portions of sodium borohydride solution were added 2 hours, 4 hours and 10 hours after the first addition of borohydride solution. After 10 more hours at 0°, 20 g. of sodium hydroxide pellets was added and the solution was evaporated to 150 ml. The solution was evaporated twice more to this volume after the addition of 100-ml. portions of water. The resulting basic solution was then cooled and extracted with ether. After drying, this ethereal solution was evaporated, leaving 478 mg. (16% of the weight of the nepetalactone) of an unsaponifiable neutral oil which was discarded.

The basic aqueous solution was acidified with 6 *N* hydrochloric acid and extracted with ether. After 2 hours, the ethereal solution was extracted with sodium bicarbonate solution. The ether solution was dried and then evaporated, leaving 1.422 g. (51%) of the nepetolactones VIIa and b, $n^{25}D$ 1.4619. After one evaporative distillation, a sample was found to contain 70.25% C and 9.25% H (calcd., 70.10% and 9.15%) and had an infrared spectrum quite similar to that of nepetolactones obtained by the alkaline hydrogen peroxide oxidation of nepetalic acid.

The bicarbonate solution was acidified and extracted with ether. Evaporation gave 876 mg. of acidic material, which was chromatographed on silicic acid. Elution with 3% methanol in chloroform gave a succession of crystalline fractions which were combined, giving 798 mg. (26%) of a nepetolic acid mixture (Vc and c′), m.p. 93–100°. Recrystallization of a portion of this mixture from chloroform–petroleum ether gave a pure isomer, Vc, m.p. 139–140°; the yield of this isomer represented 21% of the acid mixture. The infrared spectrum of this nepetolic acid showed a hydroxyl band at 2.95 μ; it differed considerably from the spectrum of *trans-trans*-nepetolic acid[4] (Vd).

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36; neut. equiv., 172. Found: C, 62.98; H, 9.27; neut. equiv., 172.

Oxidation of Nepetolic Acid, M.p. 106° (Vd) to *trans-trans*-Nepetonic Acid (IId).—A 31-mg. sample of Vd, m.p. 105–106°, was dissolved in 0.5 ml. of acetone (distilled from calcium chloride, then from potassium permanganate) and titrated at room temperature with an aqueous solution of chromic acid and sulfuric acid as described by Jones.[14] The color due to excess reagent was dispelled by a drop of isopropyl alcohol, and then 5 ml. of ether and 100 mg. of magnesium sulfate added. The inorganic salts were filtered off and washed well with ether. Evaporation of the ether left *trans-trans*-nepetonic acid (IId) in quantitative yield. This ketoacid was treated in a centrifuge tube with a freshly prepared solution of 60 mg. of 2,4-dinitrophenylhydrazine, 0.3 ml. of sulfuric acid and 0.45 ml. of water in 1.5 ml. of 95% ethanol. After half an hour the tube was centrifuged, the liquid removed with a pipet, and the precipitate washed three times with 5-ml. portions of water. It was then recrystallized once from ethanol–water, yielding 56.9 mg. (90%) of the 2,4-dinitrophenylhydrazone of IId, m.p. 173.5–175°; this product gave no depression in a mixed melting point determination with an authentic sample.[4]

Oxidation of Nepetolic Acid, M.p. 140° (Vc) to *trans-cis*-Nepetonic Acid (IIc).—An 18-mg. sample of Vc, m.p. 139–140°, was oxidized as described above. The product (IIc) was chromatographed on silicic acid and then evaporatively distilled at 100° (0.1 mm.) for an analytical sample, $n^{25}D$ 1.4678. The infrared spectrum of this keto acid (liquid film) was quite similar to that of the *trans-trans* isomer IId; the principal difference was a peak at 7.8 μ which was found only in the spectrum of IIc.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.49; H, 8.29. Found: C, 63.67; H, 8.10.

A sample of IIc was converted to *trans-cis*-nepetonic acid 2,4-dinitrophenylhydrazone, m.p. 171–172°, in 82% yield based on Vc. A mixed melting point with the corresponding derivative of IId was 148–156°.

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: C, 51.42; H, 5.18; N, 15.99. Found: C, 51.44; H, 5.32; N, 16.28.

This new 2,4-dinitrophenylhydrazone also was prepared in 73% yield from the nepetolic acid mixture, m.p. 93–100°, obtained from the sodium borohydride reduction of the ozonized nepetalactone.

Oxidation of *trans-cis*-Nepetonic Acid (IIc) to *trans-cis*-Nepetic Acid (Ic).—To a 43-mg. sample of IIc in a centrifuge tube was added first 4 ml. of 10% sodium hydroxide solution and then a solution of 800 mg. of iodine and 1.6 g. of potassium iodide in 6.4 ml. of water. After stirring for half an hour, the precipitated iodoform was separated by centrifugation and decantation. The aqueous solution was treated with 400 mg. of sodium bisulfite, acidified with 6 *N* hydrochloric acid, and continuously extracted with ether overnight. The solid residue from evaporation of the ether was chromatographed on silicic acid and the series of crystalline fractions combined and recrystallized from chloroform–petroleum ether, giving 20.3 mg. of Ic, m.p. 114–115°, $[\alpha]^{21}D$ +85.8° (5.54 mg./ml.), ($CHCl_3$) (47% from Vc). A mixed melting point with *trans-trans*-nepetic acid (Id) was 99–107°.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.03; neut. equiv., 86. Found: C, 55.77; H, 7.13; neut. equiv., 86.

This new nepetic acid was also prepared from the nepetolic acid mixture, m.p. 93–100°, in 48% yield.

For comparison purposes dimethyl *trans-cis*-nepetate was prepared with diazomethane in the usual way and evaporatively distilled at 65° (0.1 mm.), $n^{25}D$ 1.4485. The infrared spectrum of this ester was practically identical with that of *dl-trans-cis*-dimethyl 3-methylcyclopentane-1,2-dicarboxylate.[3]

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.00; H, 8.05. Found: C, 59.28; H, 7.90.

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[14] E. R. H. Jones, *et al.*, *J. Chem. Soc.*, 2555 (1953).