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

The Constituents of the Volatile Oil of Catnip. III. The Structure of Nepetalic Acid and Related Compounds[1]

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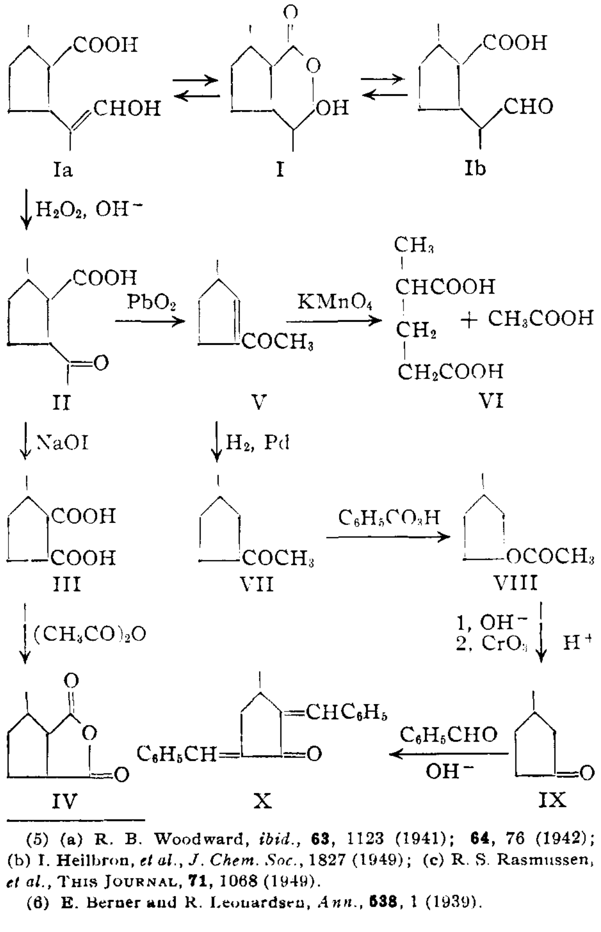
Nepetalactone (XI), the principal constituent of the volatile oil of catnip, on hydrolysis yields two epimeric nepetalic acids (Ib and Ib′), which are shown to be cyclopentanes substituted in the 1-, 2- and 3-positions with $-CH_3$, -COOH and $-CH(CH_3)CHO$, respectively. The orientation of these substituents in the natural compounds and their degradation products are 1,2-*cis* and 2,3-*trans*. The *trans*-arrangement of the 1- and 3-substituents makes possible the facile epimerization of the 2-substituent, in the form of an ester or anhydride, to yield members of an unnatural series with a 1,2-*trans* and 2,3-*cis* arrangement of the three substituents on the cyclopentane nucleus.

In the first paper[2] of this series it was shown that nepetalic acid, the acidic compound that may be extracted from the volatile oil of catnip with base, is a trisubstituted cyclopentane containing $-CH_3$, -COOH and $-CH(CH_3)CHO$ as the substituent groups. The latter two functional substituents were assigned adjacent positions in the ring because (a) the chemical properties of nepetalic acid indicated that it existed in the three tautomeric forms I, Ia and Ib, and (b) its degradation *via* II gave a dibasic acid III which readily formed an anhydride (IV). The position of the methyl substituent was not determined, but its presence was inferred from the C-methyl values of nepetalic acid and its degradation products; a recent study[3] of the C-methyl determination has confirmed the earlier conclusion that these compounds are methylcyclopentane derivatives.

Further work on this problem, which is now reported, (a) definitely establishes the structure of nepetalic acid, m.p. 73–75°, $[\alpha]^{30}_D$ +39.8° (1.0 in C_2H_5OH) and +47.6° (1.0 in $CHCl_3$), as the lactol I, in tautomeric equilibrium with the aldehydo forms Ia and Ib, and (b) shows the stereochemical relationships of the three substituents of the cyclopentane nucleus in I and its significant degradation products.

The infrared spectrum of a chloroform solution as well as a solid film of nepetalic acid (I) has absorption bands at 3.04 and 5.85 μ, which are characteristic of the hydroxy lactone structure I. The reactions by which the positions of the ring substituents of I were fixed involved a degradation of nepetonic acid (II) which is obtained by the hydrogen peroxide oxidation of nepetalic acid,[2] presumably the form Ia. When nepetonic acid was heated with lead dioxide, an adaptation of Doering's oxidative bis-decarboxylation of 1,2-dicarboxylic acids,[4] an oxidative decarboxylation occurred with the elimination of the elements of formic acid and the α,β-unsaturated ketone V was produced in 34% yield. The structure of this ketone was established by analyses and spectra; the ultraviolet spectrum was in agreement with Woodward's rules,[5a] and together with the spectra of its semicarbazone and its red 2,4-dinitrophenylhydrazone agreed closely with the values for 1-acetylcyclopentene[5b]; the infrared spectrum of V showed the carbonyl band displaced to 6.03 μ as would be expected for an α,β-unsaturated ketone.[5c]

The ketone V was oxidized in 58% yield to (+)-α-methylglutaric acid[6] (VI), the infrared spectrum of which is identical with that of authentic *dl*-α-methylglutaric acid. The ketone V was further degraded *via* VII and VIII to 3-methylcyclopentanone (IX), which was isolated as the optically active dibenzylidene derivative (X). The infrared spectra of X and an authentic sample of *dl*-2,5-dibenzylidene-3-methylcyclopentanone were indistinguishable; also the ultraviolet spectra of these



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[1] Presented at the Roger Adams Symposium of Chemistry, Urbana, Ill., September 2–4, 1954.

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

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

[4] W. von E. Doering, M. Farber and A. Sayigh, *ibid.*, **74**, 4370 (1952).

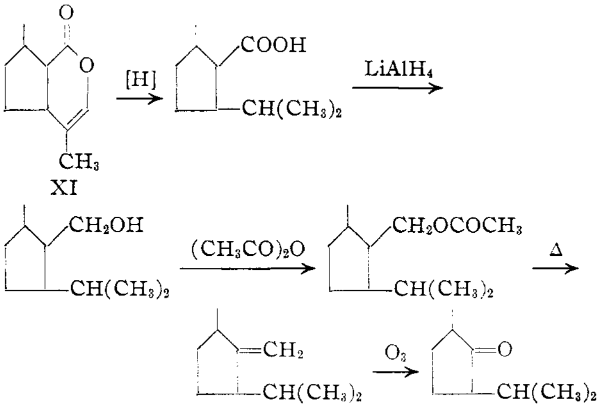
[5] (a) R. B. Woodward, *ibid.*, **63**, 1123 (1941); **64**, 76 (1942); (b) I. Heilbron, *et al.*, *J. Chem. Soc.*, 1827 (1949); (c) R. S. Rasmussen, *et al.*, THIS JOURNAL, **71**, 1068 (1949).

[6] E. Berner and R. Leonardsen, *Ann.*, **538**, 1 (1939).

compounds were in agreement with reported values for the *dl*-compound.[7]

The conversion of the ketone V to both VI and X establishes the relative positions of the three substituents on the cyclopentane nucleus of nepetonic acid and its precursor nepetalic acid as those shown in II and I, respectively. The earlier degradation[2] of II, *via* the haloform reaction, to an optically active nepetic acid (III) and anhydride (IV) is in accord with the structural data derived from the ketone V.

Meinwald recently reported[8] a similar conclusion in regard to the position of the methyl group in nepetalactone[2] (XI), the dehydration product of the lactol I. He degraded this lactone *via* the sequence shown below to 2-methyl-5-isopropylcyclopentanone and compared its spectrum and derivatives with those of a synthetic sample of this ketone.



XI

Stereochemical Considerations.—In the earlier work[2] it was observed that a large portion (at least 45%) of the oil of catnip consisted of nepetalactone (XI) and that the free nepetalic acid which may be extracted from the oil with sodium bicarbonate solution was formed probably by hydrolysis of this lactone during the steam distillation of the oil from the plant. When this lactone is opened by this hydrolysis or by the saponification that results from the extraction of the oil with sodium hydroxide solution, two nepetalic acids, Ib and Ib′, epimeric at the newly created asymmetric center result. One of these is the solid acid, m.p. 73–75°, which has been oxidized[2] to a nepetalinic acid XII, m.p. 85°. This dibasic acid was converted by diazomethane to a dimethyl ester XIII which is identical (infrared spectrum) with the diester prepared *via* XIV and XV. The preparation of XIII with the mild reagents of this latter sequence shows that each of the four asymmetric centers of Ib remains intact when it is oxidized directly to XII with chromic acid.

An investigation of the acidic residues remaining from the preparation of nepetonic acid (II) by oxidation of sodium nepetalate with hydrogen peroxide led to the isolation of both XII and the epimeric nepetalinic acid XIIa, m.p. 117°, which is the oxidation product of the nepetalic acid Ib′. Indeed, both of these nepetalinic acids have been separated from the acidic fraction extracted directly from the oil of catnip; this fact supports the view that the epimeric nepetalic acids, which yield these dibasic acids by air oxidation, are present in the oil from hydrolysis of nepetelactone (XI). The separation of the nepetalinic acids XII and XIIa is facilitated by the insolubility of the barium salt of XII in water. The epimeric dimethyl nepetalinates (XIII and XIIIa) show marked differences in their infrared spectra in the region of 7–15 μ.

When heated with acetyl chloride, both XII and XIIa yielded anhydrides which completely reverted to the original acids on hydrolysis. Each of these anhydrides showed the twin absorption bands at 5.57 and 5.67 μ in their infrared spectra that are characteristic of glutaric anhydrides.[9] The acids XII and XIIa also formed anhydrides on heating to 180–250°. However, these anhydrides, which had similar but not identical infrared spectra and specific rotations, gave mixtures of acids on hydrolysis. From the hydrolysis of the pyrolytic anhydride of XII three different nepetalinic acids, XII, XIIa and XIIb, m.p. 115°, were separated. Hydrolysis of the anhydride from XIIa yielded XII and XIIa.[10]

Epimerization of the half-ester XV with sodium methoxide in methanol, followed by a saponification gave XII (57%) and XIIb (38%). This high recovery of pure acids shows that XII and XIIb are epimeric at the 2-position of the cyclopentane ring and that only this position was affected by the basic reagent. A fourth nepetalinic acid, XIIc, m.p. 111°, together with XIIb was separated from the mixture of acids resulting from the treatment of the diester XIII with sodium methoxide in methanol followed by saponification. The melting point of any of these four nepetalinic acids was depressed greatly by admixture of any other of these acids.

If it is assumed that none of these transformations of the nepetalinic acids affected the asymmetric centers of the ring carrying the –CH_3 and the –$CH(CH_3)COOH$ substituents, then the four possible nepetalinic acids have been isolated. Two of these acids have the –COOH and –$CH(CH_3)$-COOH substituents in the *trans* arrangement as in XII and XIIa and the other two have these substituents in the *cis* arrangement as in XIIb and XIIc. The fact that XII may be transformed readily into the other three nepetalinic acids shows that the 1- and 3-substituents (–CH_3 and –CH-(CH_3)COOH) in the stable asymmetric centers *are oriented trans to each other*. If these two groups were in the *cis* arrangement, only two nepetalinic acids epimeric at the asymmetric center in the 3-substituent (–$\overset{*}{C}H(CH_3)COOH$) and with the stable *trans–trans* arrangement of the three ring substituents should have resulted from the base-catalyzed epimerization reactions described above.[10a]

The orientation of the 2-carboxy substituent relative to the 1- and 3-substituents was indicated by

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[7] H. S. French and L. Wiley, This Journal, **71**, 3702 (1949).

[8] J. Meinwald, *Chemistry & Industry*, 488 (1954); since the manuscript of the present paper was prepared a more detailed report of Meinwald's work has appeared in This Journal, **76**, 4571 (1954).

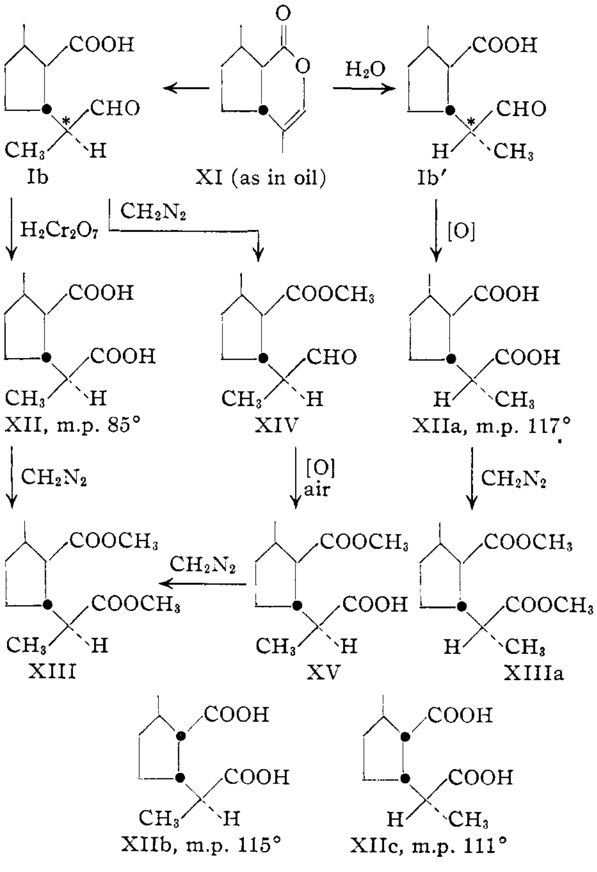
[9] G. Stork and R. Breslow, *ibid.*, **75**, 3291 (1953).

[10] A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 956 (1934), found that pyrolysis of either *cis*- or *trans*-2-carboxycyclopentaneacetic acid at 240° for 10 minutes produced an equilibrium mixture containing 86% *cis*-anhydride.

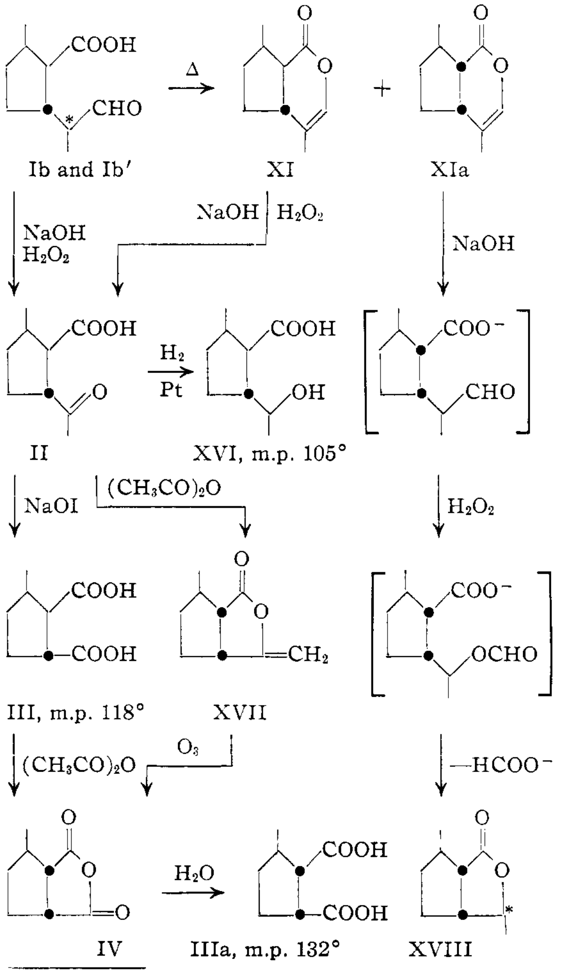
[10a] *Cf.* T. L. Jacobs and W. H. Florsheim, This Journal, **72**, 256 (1950).

the oxidation products of the nepetalic acids derived from the natural and synthetic nepetalactones. The hydrogen peroxide oxidation of nepetalic acid as extracted from the oil by base—it was pointed out earlier that the major portion of this acid comes from the saponification of nepetalactone—removes one carbon and the asymmetric center of the side chain to give nepetonic acid (II). The yield of this acid usually amounted to 60–65% and together with the nepetalinic acids, XII and XIIa, isolated from the acidic fraction after the removal of II accounted for approximately 80% of the nepetalic acid used. Hydrogenation converted II to a hydroxy acid XVI, m.p. 105°, that could be distilled without change and for which the name *trans-nepetolic acid* is proposed. The failure of this acid to form a lactone indicates the *trans* orientation of its 2,3-ring substituents. The same orientation may also be assigned to the precursors of XVI, I and II.

Nepetic acid III should have the same *cis*, *trans* arrangement of the ring substituents as II, but the anhydride IV derived from it would be expected to have the *cis* ring juncture in order to accommodate the fusion of two five-membered rings. This anhydride, which has the characteristic succinic anhydride absorption bands at 5.40 and 5.63 μ in the infrared,[9] yielded the *cis*-nepetic acid (IIIa) on hydrolysis. The same *cis*-anhydride IV resulted from the ozonolysis of the methylene lactone XVII, which was formed by the action of acetic anhydride on nepetonic acid (II). The *cis* acid IIIa was distinguished readily from the *trans* isomer III by the insolubility of the barium salt of the former[11] and also by the ease of anhydride formation. The *cis*-acid was converted to the anhydride at 150°, while the *trans* form III remained stable up to 250°.



When nepetonic acid (II) was prepared from the nepetalactone obtained from the pyrolysis of nepetalic acid—this pyrolysis requires a temperature of 250°—the yield of II dropped to 30–40% and a lower boiling neutral product *cis*-nepetolactone (XVIII) was isolated in 20–25% yield. This lactone is a liquid, b.p. 75° (0.2 mm.), which shows the charactersitic γ-lactone absorption band at 5.7 μ in the infrared.[12] The formation of this lactone indicates that the pyrolysis of nepetalic acid had caused a partial epimerization of the asymmetric center carrying the carboxyl substituent with the resultant formation of two nepetalactones XI and XIa. While the nepetalactone with the *trans* ring juncture gave nepetonic acid (II) on oxidation with alkaline hydrogen peroxide, XIa, which has the *cis* ring juncture, was converted to the *cis*-nepetolac-



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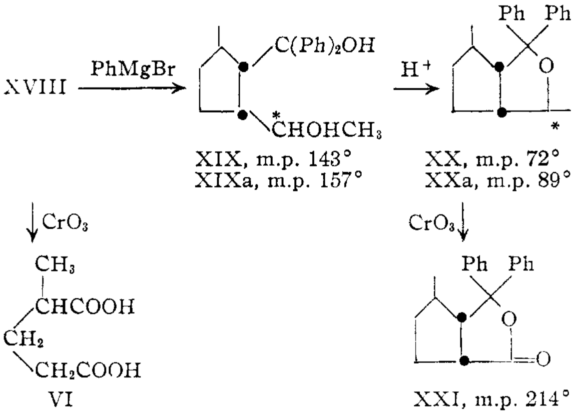
(11) This difference in the solubilities of the barium salts of the *cis*- and *trans*-nepetic acids also has been observed in this Laboratory with maleic and fumaric acids as well as with the *cis*- and *trans*-1-methylcyclopentane-1,2-dicarboxylic acids and the cyclohexane-1,2-dicarboxylic acids. However, the barium salts of both *cis*- and *trans*-cyclobutane-1,2-dicarboxylic acids, which were kindly supplied by Dr. E. R. Buchman of the Department of Chemistry of the California Institute of Technology, are water soluble.

(12) R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

tone (XVIII) and the formate anion, probably *via* the bracketed intermediates. The ready formation of the two nepetalactones XI and XIa from the pyrolysis of nepetalic acid and of the *cis*-nepetic anhydride (IV) from the *trans*-nepetonic (II) and nepetic (III) acids further substantiate the *trans*-orientation of the 1- and 3-substituents of nepetalic acid, which was deduced earlier from the epimerization of the nepetalinic acids XII and XIIa.

The lactone XVIII was shown to be a mixture of diastereoisomers epimeric at the starred asymmetric center by the sequence of reactions leading to the lactone XXI. Phenylmagnesium bromide converted XVIII to two glycols, XIX and XIXa, which were dehydrated by *p*-toluenesulfonic acid in refluxing benzene to the cyclic ethers XX and XXa. Vigorous oxidation of these cyclic ethers, whose infrared and ultraviolet spectra exclude the alternate unsaturated alcohol structure, eliminated the asymmetric center and converted them to a single lactone XXI.



XIX, m.p. 143°
XIXa, m.p. 157°

XX, m.p. 72°
XXa, m.p. 89°

VI

XXI, m.p. 214°

The lactone XVIII was oxidized to (+)-α-methylglutaric acid (VI) by chromium trioxide in acetic acid. This conversion relates XVIII to *trans*-nepetonic acid (II), which was converted to this glutaric acid *via* the α,β-unsaturated ketone V.

Acknowledgment.—The authors are indebted to Dr. Howard Burkett for the preparation and characterization of the methylene lactone (XVII) and its conversion to *cis*-nepetic acid (IIIa)[13] and to Mr. Robert W. Radue[14] for the isolation and identification of *cis*-nepetolactone (XVIII).

Experimental

3-Methylcyclopentenyl Methyl Ketone (V).—In a 100-ml. three-necked flask equipped with a pressure equalized dropping funnel, an inlet tube for nitrogen and an outlet tube connected to a Dry Ice–acetone trap was placed 15 g. of lead dioxide.[4] After the system was well swept with nitrogen a few drops of a 2.85-g. sample of nepetonic acid (II)[2] was added to the lead dioxide from the dropping funnel and the mixture slowly heated in an oil-bath to 132° at which temperature decomposition of II began. An aspirator was attached to the Dry Ice trap and the remaining nepetonic acid (II) was added dropwise to the lead dioxide with gradual increase in temperature to 150°.[15] The product was removed from the Dry Ice trap, taken up in ether, dried over anhydrous magnesium sulfate and filtered. Distillation yielded 0.83 g. (34% yield) of **3-methylcyclopentenyl methyl ketone** (V) as a colorless, mobile oil, b.p. 63° (10 mm.), $n^{25}\text{D}$ 1.4714, $[\alpha]^{25}\text{D}$ −177.5° (*c* 0.922, $CHCl_3$), $\lambda_{\max}^{\text{EtOH}}$ (ε) 237 mμ, log ε 4.24[5a,5b]. The infrared spectrum shows the carbonyl band displaced to 6.03 μ and also contains the expected band at 6.2 μ assigned to the double bond of an α,β-unsaturated ketone[5c]; V showed a C-methyl value of 1.55.

Anal. Calcd. for $C_8H_{12}O$: C, 77.40; H, 9.74. Found: C, 77.03; H, 9.75.

The 2,4-dinitrophenylhydrazone of V was prepared and recrystallized from 95% ethanol as deep red needles, m.p. 179–180°, $[\alpha]^{27}\text{D}$ −64.6° (*c* 0.176, $CHCl_3$), $\lambda_{\max}^{\text{CHCl}_3}$ 257 mμ, log ε 4.2 and 380 mμ, log ε 4.5.[5b]

Anal. Calcd. for $C_{14}H_{16}O_4N_4$: C, 55.25; H, 5.30; N, 18.42. Found: C, 55.39; H, 5.27; N, 18.33.

The semicarbazone of V was prepared and recrystallized from 95% ethanol as colorless crystals, m.p. 195–197°, $[\alpha]^{27}\text{D}$ −150.1° (*c* 0.359, $CHCl_3$), $\lambda_{\max}^{\text{CHCl}_3}$ 264 mμ, log ε 4.45.[5b]

Anal. Calcd. for $C_9H_{15}ON_3$: C, 59.61; H, 8.34. Found: C, 59.97; H, 8.21.

Oxidation of V to (+)-α-Methylglutaric Acid (VI).—To 748 mg. of V was added 760 ml. of 0.1 *N* potassium permanganate solution in small portions with a brief warming period on the steam-bath to complete the oxidation. The reaction mixture was brought to phenolphthalein end-point with 3.3 ml. of 0.1248 *N* sodium hydroxide solution and the manganese dioxide removed by centrifugation. The calculated volume of acid (6.9 ml. of 0.310 *N* sulfuric acid solution) was added and the solution concentrated to a small volume by distillation under diminished pressure. The distillate was neutralized with 39.0 ml. of 0.1248 *N* sodium hydroxide solution, evaporated to dryness yielding 395 mg. of solid material from which a *p*-phenylphenacyl ester was prepared which showed no depression in m.p. (110–111°) on admixture with authentic *p*-phenylphenacyl ester of acetic acid.

The gummy solid (518 mg.) resulting from ether extraction of the non-volatile residue was precipitated as the copper salt[16] and on regeneration with dilute sulfuric acid afforded a solid acid which on sublimation gave crystalline (+)-α-**methylglutaric acid** (**VI**), m.p. 81–82°, $[\alpha]^{25}\text{D}$ +18° (*c* 6.87, $CHCl_3$).[6] The infrared spectra ($CHCl_3$) of VI and of an authentic sample of *dl*-α-methylglutaric acid were indistinguishable; VI contained 49.05% C and 6.78% H and showed a neutral equivalent of 73 and C-methyl of 0.40 (calcd. 49.35%, 6.90%, 73 and 1.0).

(+)-2,5-Dibenzylidene-3-methylcyclopentanone (X).—A 1.77-g. sample of V absorbed one equivalent of hydrogen at 38 p.s.i. in the presence of 0.2 g. of 10% palladium-on-strontium carbonate catalyst. After removal of the catalyst, the product was distilled to give 3-methylcyclopentyl methyl ketone (VII), b.p. 53° (10 mm.), $[\alpha]^{25}\text{D}$ +8.05° (*c* 5.06, $CHCl_3$). **The 2,4-dinitrophenylhydrazone of VII** after recrystallization from 95% ethanol gave yellow needles, m.p. 98–99°.

Anal. Calcd. for $C_{14}H_{18}O_4N_4$: C, 54.89; H, 5.92. Found: C, 54.96; H, 6.05.

A 1.22-g. sample of VII was treated with 27 ml. (0.0145 mole) of perbenzoic acid in moist chloroform solution[17] at room temperature in the dark for ten days. The product, **3-methylcyclopentyl acetate** (**VIII**), was freed of acidic material by washing with saturated bicarbonate solution. Saponification after removal of solvent was affected by heating for 2 hours with 25 ml. of 10% sodium hydroxide to which was added 10 ml. of methanol. The alkaline solution was steam distilled (250 ml. collected) the distillate was saturated with salt and extracted with ether, the ether solution was dried over anhydrous magnesium sulfate, filtered and distilled. The residual 3-methylcyclopentanol was dissolved in 20 ml. of purified acetone and directly oxidized by titrating with 0.35 ml. of 8 *N* chromic acid solution[18] at 20° to the first permanent orange color. A drop of iso-

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[13] This work was done in 1942.

[14] Robert W. Radue, M.S. Thesis, University of Wisconsin, 1950.

[15] Although this decomposition temperature is 100° below that reported by Doering[4] for 1,2-dicarboxylic acids it is strongly recommended that precautions be taken in decarboxylating γ-keto acids with lead dioxide as a vigorous explosion occurred on heating these reactants to 250°.

[16] F. Tiemann and W. Semmler, *Ber.*, **31**, 2889 (1898).

[17] S. L. Friess and R. Pinson, This Journal, **74**, 1302 (1952).

[18] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

propyl alcohol was added to consume excess reagent and a few mg. of sodium bicarbonate was added with no visible reaction. The green chromium salts were removed by filtration and washed with two small portions of acetone. Benzene was added and the acetone distilled out until the distillate showed a negative 2,4-dinitrophenylhydrazone test. The remainder of the benzene was distilled and the cooled product, **3-methylcyclopentanone (IX)**, was treated with 1.0 g. of freshly distilled benzaldehyde, 10 ml. of 10% sodium hydroxide and 8 ml. of 95% ethanol.[19] The precipitate was 1.109 g. (42% over-all yield from V) of **(+)-2,5-dibenzylidene-3-methylcyclopentanone (X)**. Recrystallization from 95% ethanol afforded pale yellow needles, m.p. 152–154°, $[\alpha]^{27}\mathrm{D}$ +51.5° (*c* 1.733, $CHCl_3$), $^{\mathrm{EtOH}}_{\mathrm{max}}$ 232 mμ, log ε 4.17 and 350 mμ, log ε 4.78.[7]

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.55; H, 6.61. Found: C, 87.94; H, 6.71.

A sample of *dl*-2,5-dibenzylidene-3-methylcyclopentanone,[7] m.p. 156–158°, was prepared. When mixed with X the m.p. was depressed about 6°; the ultraviolet and infrared spectra of these two compounds, however, were indistinguishable.

Nepetalinic Acids (XII and XIIa).—Nepetalinic acid[2] (XII), m.p. 85°, $[\alpha]^{25.5}\mathrm{D}$ +30.2° (*c* 2.44, $CHCl_3$) forms a water-insoluble tetrahydrated salt when neutralized with a saturated solution of barium hydroxide. A sample of this salt after drying at room temperature over phosphorus pentoxide gave the following analyses; analyses of these barium salts require that the sample be mixed with vanadium pentoxide.

Anal. Calcd. for $C_{10}H_{14}O_4Ba{\cdot}4H_2O$: C, 29.70; H, 5.45. Found: C, 29.15; H, 5.89.

When this salt was dried at 120° (0.1 mm.) for 18 hours it became anhydrous.

Anal. Calcd. for $C_{10}H_{14}O_4Ba$: C, 35.80; H, 4.21. Found: C, 35.10; H, 4.63.

The nepetalinic acid was recovered readily from the hydrated barium salt with dilute hydrochloric acid followed by extraction with ether.

By use of the insoluble barium salt it was possible to obtain 7–10% yields of XII from the acidic residue remaining from the preparation of nepetonic acid (II).[2] A second nepetalinic acid was obtained in lower (*ca.* 3–5%) yield from the water solution after the removal of the barium salt of XII. This acid, whose barium salt is water soluble, was isolated and purified by a combination of precipitation of an insoluble lead salt, regeneration with dilute hydrochloric acid, sublimation and recrystallization from ether and petroleum ether to give a nepetalinic acid (XIIa) as colorless needles melting at 115–117°, $[\alpha]^{27.5}\mathrm{D}$ +16.2 (*c* 1.25, $CHCl_3$).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00; neut. equiv., 100. Found: C, 60.04; H, 8.07; neut. equiv., 101.

Separation of XII and XIIa from Oil of Catnip.—A 640-mg. sample of the acidic material extracted from oil of catnip with sodium bicarbonate solution was dissolved in 5 ml. of benzene and added to a 1.5 × 30 cm. column of Florex (XS 20, 60 mesh). Elution with 200 ml. of benzene yielded: 56 mg. of nepetalic anhydride,[20] m.p. 140°; with 600 ml. of 16% ether in benzene yielded 127 mg. of nepetalic acid (positive reaction with 2,4-dinitrophenylhydrazone); with 175 ml. of 16% ether in benzene yielded 127 mg. of nepetalinic acid (XIIa), m.p. 117°. Nepetalinic acid (XII), m.p. 85°, did not crystallize in the above separation, but its presence was established by neutralizing a second sample of bicarbonate extracted acidic fraction of oil of catnip (640 mg.) with a saturated solution of barium hydroxide. From the insoluble barium salt that separated 97 mg. of XII was obtained.

Methyl Nepetalate 2,4-Dinitrophenylhydrazone.—Methyl nepetalate (XIV) was prepared as previously described by treating an ether solution of nepetalic acid (I), m.p. 73–75°, $[\alpha]^{28}\mathrm{D}$ +50° (*c* 5.66, $CHCl_3$) with diazomethane.[2] The 2,4-dinitrophenylhydrazone of methyl nepetalate (XIV) was prepared and recrystallized from aqueous methanol to give yellow-orange needles melting at 109–110°, $[\alpha]^{27}\mathrm{D}$ +30.2° (*c* 0.57, $CHCl_3$), $\lambda^{\mathrm{CHCl_3}}_{\mathrm{max}}$ 258 mμ, log ε 4.02 and 3.55 mμ, log ε 4.35.

Anal. Calcd. for $C_{17}H_{22}O_6N_4$: C, 53.95; H, 5.86. Found: C, 53.98; H, 5.59.

Methyl Nepetalinate (XV).—The air oxidation of XIV was carried out by passing a slow stream of air (dried by bubbling through concentrated sulfuric acid and then through a soda-lime tube) through the side arm of a 50-ml. round-bottomed flask over a magnetically stirred sample (2.84 g.) of XIV and finally venting through a water-cooled condenser. The course of the oxidation was followed by the neutral equivalent of the material; 32 hours was required to produce the neutral equivalent of XV. The flask contents and the residues from the neutral equivalent determinations were combined, acidified, extracted with ether and the ether layer extracted with a saturated sodium bicarbonate solution. The bicarbonate extract was acidified, extracted with ether, dried and distilled to give methyl nepetalinate (XV), b.p. 125–127° (0.18 mm.), $n^{25}\mathrm{D}$ 1.4618, $[\alpha]^{27}\mathrm{D}$ −36.1° (*c* 2.26, $CHCl_3$).

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47; neut. equiv., 214. Found: C, 61.35; H, 8.52; neut. equiv., 213.5.

Dimethyl Nepetalinate (XIII).—This ester was prepared by treating XV with diazomethane. The product distilled at 89° (0.9 mm.), $n^{25}\mathrm{D}$ 1.4492, $[\alpha]^{28}\mathrm{D}$ −56.5° (*c* 2.71, $CHCl_3$). The over-all yield of XIII from nepetalic acid (I) *via* XIV and XV was 91.8%.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.12; H, 8.83. Found: C, 63.35; H, 8.82.

The diester XIII also was prepared by treating an ether solution of 4.34 g. of nepetalinic acid[2] (XII) with diazomethane. This ester distilled at 87° (1.3 mm.), $n^{25}\mathrm{D}$ 1.4493, $[\alpha]^{25.5}\mathrm{D}$ −58.9° (*c* 2.39, $CHCl_3$).

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.13; H, 8.78.

The infrared spectrum of XIII (pure liquid in a 0.025 mm. cell) prepared from XII was identical with that prepared from nepetalic acid (I) *via* XIV and XV.

Dimethyl Nepetalinate (XIIIa).—A 692-mg. sample of nepetalinic acid (XIIa), dissolved in ether, was treated with diazomethane. After removal of the solvent the residue was evaporatively distilled at 44° (0.05 mm.), $n^{25}\mathrm{D}$ 1.4492, $[\alpha]^{25.5}\mathrm{D}$ +25.1° (*c* 2.02, $CHCl_3$).

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.40; H, 8.71.

The infrared spectrum of XIIIa (liquid in a 0.025-mm. cell) was distinctly different from that of XIII in the region of 7–15μ.

Anhydrides of XII and XIIa.—A 4.017-g. sample of XII was dissolved in 50 ml. of acetyl chloride and the solution refluxed gently on the steam-bath for 45 minutes. The acetyl chloride and acetic acid were removed and the product distilled to give a nepetalinic anhydride, b.p. 121–122° (1.0 mm.), $[\alpha]^{26.5}\mathrm{D}$ +48.4° (*c* 4.34, $CHCl_3$), $n^{25}\mathrm{D}$ 1.4772.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74; neut. equiv., 91. Found: C, 66.13; H, 7.74; neut. equiv., 92.5.

The infrared spectrum (chloroform) of this anhydride had the characteristic twin bands at 5.57 and 5.67 μ of a glutaric anhydride.[9] Neutralization of this anhydride with a saturated solution of barium hydroxide and regeneration of the acid from the water-insoluble barium salt yielded a practically quantitative recovery of nepetalinic acid (XII), m.p. 83–85°, which showed no depression in melting point on admixture with authentic material.

A 190-mg. sample of nepetalinic acid (XIIa) similarly treated with 15 ml. of acetyl chloride gave an anhydride that evaporatively distilled at 65° (0.2 mm.) as colorless liquid. The infrared spectrum (chloroform) of this anhydride also showed the characteristic twin bands of a glutaric anhydride at 5.57 and 5.67 μ[9] and was similar to but not identical with that of the anhydride from the acid XII. There was no evidence of the carboxyl group absorption in the 3–3.4 μ and 5.85 μ regions. A 132-mg. sample of this anhydride was warmed in a tightly stoppered flask with 5 ml. of distilled water at 80° for 24 hours. Evaporation of the water left the crystalline nepetalinic acid (XIIa), m.p. 116–117°.

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[19] A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 167.

[20] S. M. McElvain, P. M. Walters and R. D. Bright, THIS JOURNAL, **64**, 1828 (1942).

Pyrolytic Anhydrides from XII and XIIa.—A 4.017-g. sample of nepetalinic acid (XII), m.p. 83–85°, was heated in a metal-bath at 250° until water no longer appeared in the condenser (30 min.). The product was distilled to give 2.61 g. (70.2%) of nepetalinic anhydride boiling at 121–123° (1.0 mm.), $n^{25}\text{D}$ 1.4772, $[\alpha]^{25.5}\text{D}$ +36.3°, neut. equiv. 92.5 (calcd. 91). Its infrared spectrum (chloroform) contained bands at 5.57 μ and 5.67 μ characteristic of a glutaric anhydride,[9] but differed in the 7–15 μ region from the spectra of the anhydrides of XII and XIIa prepared with acetyl chloride.

A 1.835-g. sample of the anhydride yielded 2.42 g. (58.5%) of water-insoluble barium salt from which was recovered nepetalinic acid (XII), m.p. 83–85°. The filtrate of water-soluble barium salts was acidified and extracted with ether. The dried ether extract yielded 668 mg. (30.6%) of a mixture of acids, from which nepetalinic acid (XIIa), m.p. 115–117°, and a nepetalinic acid (XIIb see next section for analyses), m.p. 113–114°, were separated by fractional crystallization.

A 414-mg. sample of nepetalinic acid (XIIa) was heated for 1 hr. at 250° at one atmosphere and then evaporatively distilled at 100° (0.1 mm.) to give a nepetalinic anhydride, $[\alpha]^{25}\text{D}$ +35.7° (*c* 0.61, $CHCl_3$). The infrared spectrum (chloroform) contained the expected anhydride bands at 5.57 and 5.67 μ[9] and in general appearance very much resembled the spectrum of the anhydride obtained by pyrolysis of nepetalinic acid (XII). This anhydride also proved to be a mixture of isomers. Neutralization with a saturated solution of barium hydroxide produced a 35% yield of water-insoluble barium salt, which on regeneration gave nepetalinic acid (XII), m.p. 82–85°. The acids which gave soluble barium salts were isolated but failed to crystallize.

A 0.977-g. sample of the anhydride prepared by the action of acetyl chloride on XII was heated at 250° for 45 minutes and then evaporatively distilled at 104° (0.18 mm.), $[\alpha]^{30}\text{D}$ +42.8° (*c* 3.11, $CHCl_3$). When this anhydride was hydrolyzed and the acids separated *via* the barium salts, XII (60%) and XIIa (8%) were isolated; the remainder of the acidic material was a mixture of isomers that failed to crystallize.

Nepetalinic Acids (XIIb and XIIc).—A 1.031-g. sample of methyl nepetalinate (XV) was heated for 10.5 hours in a refluxing solution of two equivalents of sodium methoxide in 25 ml. of methanol. The methyl alcohol was removed under diminished pressure, the residue acidified with hydrochloric acid, and the organic acids extracted with ether. After removal of the ether, the acid-ester was saponified with a solution of 5 g. of barium hydroxide octahydrate in 50 ml. of water.[21] The insoluble barium salt of XII, after separation by filtration, yielded 0.547 g. (56.8%) of XII, m.p. 83–85°. From the water-soluble barium salt in the filtrate 0.371 g. (38.6%) of a third **nepetalinic acid XIIb**, m.p. 114–115°, $[\alpha]^{27}\text{D}$ +19.1° (*c* 2.50 $CHCl_3$), was isolated.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00; neut. equiv., 100. Found: C, 60.15; H, 8.09; neut. equiv., 101.3.

A 1.81-g. sample of dimethyl nepetalinate (XIII) was heated in a refluxing solution of 6 g. of sodium methoxide in 55 ml. of dry methanol. Water then was added to saponify the ester and the methanol was removed by distillation until the temperature reached 98°. The solution was acidified with hydrochloric acid, extracted with ether; after drying, the ether was removed to give 1.57 g. of an oil from which 123 mg. (7.8%) of nepetalinic acid (XII), m.p. 83–85°, was recovered *via* its water-insoluble barium salt. Chromatographic separation of the remaining material on a Florex column was ineffective. However, crystallization from a mixture of ether and petroleum ether yielded 173 mg. (10.9%) of nepetalinic acid (XIIb), m.p. 113–115°, which showed no depression in melting point on admixture with authentic acid. About 200 mg. (12.6% yield) of a fourth **nepetalinic acid XIIc**, m.p. 109–111°, crystallized from the residue after removal of XII and XIIb and was purified by sublimation and recrystallization from an ether–petroleum ether mixture.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00; neut. equiv., 100. Found: C, 60.14; H, 7.94; neut. equiv., 102.

The water insolubility of the barium salt of XII facilitates the separation of this compound from the other stereoisomers XIIa, XIIb and XIIc. The infrared spectra of these acids are quite similar in the 5–6 μ region but show sufficient differences in the 7–15 μ region to indicate they are individual compounds. The melting point of any one of these nepetalinic acids, is depressed 20–30° when mixed with any other of these acids.

Nepetic Anhydride (IV). (a) **From Nepetonic Acid.**[13]—A 3.0-g. sample of nepetonic acid[2] (II) and 4.2 g. of acetic anhydride were heated at 155° for 3 hours and then distilled under diminished pressure to yield 1.36 g. (51%) of **nepetonolactone (XVII)**, b.p. 52–54° (0.05 mm.), $n^{25}\text{D}$ 1.4790–1.4799. This lactone gave a positive Legal test.[22]

A 2.5-g. sample of XVII was ozonized in the presence of 45 ml. of dry ethyl acetate until one equivalent of ozone was absorbed. The solvent was removed under diminished pressure and the ozonide shaken overnight with water. The water was extracted with ether, which then was separated, dried and distilled. A low boiling forerun of 0.28 g. (50%) of formic acid, b.p. 98–110°, $n^{25}\text{D}$ 1.3660, was collected, followed by 1.06 g. (42.4%) of nepetic anhydride (IV), b.p. 94–100° (0.1 mm.), $n^{25}\text{D}$ 1.4712–1.4721, $[\alpha]^{25}\text{D}$ +25.3°.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.40; H, 6.50; neut. equiv., 77. Found: C, 62.35; H, 6.70; neut. equiv., 82.

From the water layer formaldehyde was isolated in 3.6% yield as the dimedone derivative, which showed no depression in melting point on admixture with authentic material, m.p. 188–189°. The ozonolysis also was carried out in pentane using Raney nickel catalyst to decompose the ozonide.[23] Nepetic anhydride was isolated in 56% yield, but no formic acid or formaldehyde was found.

(b) **From *trans*-Nepetic Acid.**—A 1.32-g. sample of nepetic acid[2] (III), m.p. 115–118°, was heated with 17 ml. of freshly distilled acetic anhydride for 2.5 hours. The acetic acid and acetic anhydride were removed under diminished pressure and the nepetic anhydride (IV) was evaporatively distilled at 60° (0.1 mm.), $[\alpha]^{30}\text{D}$ +20.8° (*c* 2.66, $CHCl_3$). The infrared spectrum (chloroform) contained bands at 5.40 and 5.63 μ which are characteristic of a succinic anhydride.[9]

***cis*-Nepetic Acid (IIIa).**[13]—A 1.9-g. sample of nepetic anhydride (IV) prepared from XVII was dissolved in 12 ml. of 10% sodium hydroxide and allowed to stand for a short time. Water was added to dissolve the precipitated sodium salt, the solution was acidified with 10% sulfuric acid and extracted with ether. On removal of the ether the resulting oil solidified within 15 minutes. Two recrystallizations from an ether–petroleum ether mixture yielded 0.4 g. of *cis*-nepetic acid (IIIa), m.p. 125–126°, $[\alpha]^{25}\text{D}$ +69.1°. A mixture of III and IIIa melted at 85–93°. In the later work it was found advantageous to purify this acid *via* its water-insoluble barium salt[11]; the resulting product melted at 131–132°.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.03; C-methyl, 1.0. Found: C, 55.76; H, 7.09; C-methyl, 0.71.

A 560-mg. sample of IV prepared from nepetonic acid (II) was boiled for 2 hours with 15 ml. of water. After cooling, a saturated solution of barium hydroxide was added. The precipitate (0.879 g.) was removed by filtration and treated with dilute hydrochloric acid to yield after extraction with ether 426 mg. (68%) of solid acid, m.p. 95–102°. This acid was recrystallized from a mixture of chloroform and petroleum ether to give colorless crystals, m.p. 125–128°, which showed no depression in melting point on admixture with *cis*-nepetic acid obtained from nepetonic acid *via* nepetonolactone.

cis-Nepetic acid (IIIa), m.p. 132°, readily loses water to form the anhydride on heating to 150°, while the *trans*-nepetic acid (III), m.p. 118°, is stable to over 250°. A similar behavior was observed with the *cis*- and *trans*-1-methylcyclopentane-1,2-dicarboxylic acids where the *cis* isomer, m.p. 128–131°, decomposed to the anhydride at 135° but the *trans* isomer, m.p. 118–119°, is stable to over

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[21] These conditions do not epimerize the asymmetric center in the α-position to the free carboxyl group in the nepetalinic acids as an 80 mg. sample of nepetalinic XIIa was recovered unchanged after heating for 36 hours in a refluxing solution of 1 g. of barium hydroxide octahydrate in 5 ml. of water.

[22] W. A. Jacobs, A. Hoffmann and E. L. Gustus, *J. Biol. Chem.*, **70**, 1 (1926).

[23] N. C. Cook and F. C. Whitmore, THIS JOURNAL, **63**, 3540 (1941).

250°. It was found that a mixture of *cis*- and *trans*-1-methylcyclopentane-1,2-dicarboxylic acids also can be separated conveniently by precipitating the *cis* isomer as the water-insoluble barium salt.[11]

***cis*-Nepetolactone (XVIII).**[14]—A 16.5-g. sample of nepetalactone, prepared by the pyrolysis of nepetalic acid, was added to 180 ml. of a 10% sodium hydroxide solution. The vigorously stirred solution was cooled to 40° and 75 ml. of 30% hydrogen peroxide[24] was added dropwise at such a rate as to maintain the reaction temperature at about 50–60°. A green-yellow color developed on mixing the reactants, but this color disappeared and the temperature decreased as the reaction proceeded to completion. The reaction was allowed to stand 3 hr. then acidified to congo red with dilute hydrochloric acid, extracted with ether and the ether layer washed with several small portions of water to remove hydrogen peroxide. The ether layer then was extracted with saturated sodium bicarbonate solution to remove acidic material.

The neutral ether layer yielded nepetolactone (XVIII) in 20–25% yield as a colorless, mobile oil with a mint-like odor boiling at 74–75° (0.2 mm.), $n^{25}\text{D}$ 1.4632, d^{25}_4 1.0327, $[\alpha]^{23}\text{D}$ −8.4°.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; sapn. equiv. 154; C-methyl, 2.0, *MR*D, 41.15. Found: C, 70.15; H, 9.23; sapn. equiv., 152; C-methyl, 1.88; *MR*D 41.14.

The infrared spectrum (liquid film) of XVIII was obtained and showed the presence of a γ-lactone carbonyl band at 5.7 μ.[12]

The bicarbonate extract was acidified and extracted with ether; the ether was removed and the mixture of acids neutralized with a saturated solution of barium hydroxide which precipitated nepetalinic acid (XII) as the water-insoluble barium salt.[25] The filtrate was acidified and extracted with ether, the ether dried and removed to give a 30–40% yield of nepetonic acid (II). Nepetonic acid 2,4-dinitrophenylhydrazone was prepared by the Brady method[26] as bright yellow needles melting at 174–175°, $[\alpha]^{27}\text{D}$ −145° (*c* 0.58, $CHCl_3$), $\lambda_{\max}^{CHCl_3}$ 356, log ϵ 4.31.

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: C, 51.42; H, 5.18; N, 16.00. Found: C, 51.62; H, 5.12; N, 15.89.

Methyl nepetonate 2,4-dinitrophenylhydrazone, m.p. 105.4–105.6°, $[\alpha]^{27}\text{D}$ −165° (*c* 0.57, $CHCl_3$), $\lambda_{\max}^{CHCl_3}$ 355 mμ, log ϵ 4.35, was isolated as orange plates when II was refluxed in methanol, with 2,4-dinitrophenylhydrazine and concentrated hydrochloric acid.

Anal. Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.70; H, 5.49; N, 15.40. Found: C, 52.80; H, 5.49; N, 15.62.

Hydrogenation of Nepetonic Acid (II) to Nepetolic Acid (XVI).—Hydrogenation of 3.4 g. of nepetonic acid in 50 ml. of anhydrous ether was carried out in the presence of 0.3 g. of platinum oxide catalyst; one equivalent of hydrogen was absorbed after shaking at 37 p.s.i. for 85 minutes; no additional hydrogen was taken up on continued shaking. After removal of the catalyst by filtration, 3.5 g. of a white solid remained on evaporation of the ether. A single recrystallization from an ethyl acetate–petroleum ether mixture afforded crystals melting at 104.5–106°. This compound sublimes at 100°; a sample was sublimed at 80° (0.1 mm.) for analysis.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.75; H, 9.37; neut. equiv., 172; C-methyl, 2.0. Found: C, 62.78; H, 9.46; neut. equiv., 174; C-methyl, 1.51.

Reaction of Nepetolactone (XVIII) with Phenylmagnesium Bromide.—To a solution of phenylmagnesium bromide (0.183 mole) in ether was added dropwise 0.08 mole of XVIII dissolved in ether. No precipitate was observed, but sufficient heat was generated to keep the ether refluxing. The solution was then refluxed for 3 hours on a steam-bath. On treating the cooled viscous product with 0.4 mole of dilute hydrochloric acid, 15.7 g. (63%) of a heavy waxy precipitate separated. The crude product was separated by fractional crystallization from a mixture of ethanol and water into two isomeric **α-[2-(1-hydroxyethyl)-5-methylcyclopentyl]-benzohydrols,** XIX as white crystals, m.p. 141–143° (8% yield), and XIXa as transparent colorless prisms, m.p. 156–157.5° (13% yield). The remaining material melted at 125–135°.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.45. Found: (for XIX): C, 81.24; H, 8.56. Found (for XIXa): C, 81.08; H, 8.34.

The infrared spectra (chloroform) of these diols contained the expected hydroxyl band at 3.0 μ and in over-all appearance were very similar but not identical.

2,2-Diphenyl-4,8-dimethyl-3-oxabicyclo[3.3.0]octanes (XX and XXa).—The diols XIX and XIXa each were dehydrated to a pair of cyclic ethers XX and XXa by heating a 310-mg. sample in 50 ml. of refluxing dry benzene containing 20 mg. of *p*-toluenesulfonic acid. This procedure on XIX yielded 235 mg. (81%) of **2,2-diphenyl-4,8-dimethyl-3-oxabicyclo[3.3.0]octane (XX),** m.p. 69.8–71.9°, which readily sublimed at 65° (0.1 mm.).

Anal. Calcd. for $C_{21}H_{24}O$: C, 86.22; H, 8.27. Found: C, 86.23; H, 8.50.

The diol XIXa yielded 256 mg. (88%) of XXa, m.p. 88.5–89.5°.

Anal. Calcd. for $C_{21}H_{24}O$: C, 86.22; H, 8.27. Found: C, 86.53; H, 8.45.

The infrared spectra (chloroform) of each of these cyclic ethers showed complete absence of a hydroxyl absorption band.

Conversion of XX and XXa to 2,2-Diphenyl-4-oxo-8-methyl-3-oxabicyclo[3.3.0]octane (XXI).—A 300-mg. sample of XX was dissolved in 50 ml. of glacial acetic acid containing 333 mg. of chromium trioxide and stirred for 7 hours at 55°. The acetic acid was removed, water was added and the water extracted with benzene. The benzene was distilled to yield 251 mg. of tan colored semi-solid. Chromatographic separation on an alumina column using benzene and ether as eluants afforded 135 mg. of recovered starting material and 94 mg. (57%) of **2,2-diphenyl-4-oxo-8-methyl-3-oxabicyclo[3.3.0]octane (XXI)** as colorless needles which were observed to crumble at 170° and sublime to colorless prisms which melted sharply at 213–214°. A sample was sublimed at 140° (0.04 mm.) for analysis.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.19; H, 6.89. Found: C, 82.00; H, 6.96.

The infrared spectrum (chloroform) of XXI showed a strong band at 5.7 μ indicative of a γ-lactone.[12]

In a like manner the cyclic ether XXa was oxidized to XXI in 64% yield. There was no depression in melting point on admixture of XXI from the two sources.

Oxidation of Nepetolactone (XVIII) to VI.—A 8.12-g. sample of XVIII was dissolved in 400 ml. of acetic acid and to this solution was added 10.3 g. of chromium trioxide dissolved in 15 ml. of water. The temperature rose to 36° on mixing; it was gradually increased to 55° and held at this temperature, with stirring, for 12 hours. The acetic acid was removed under diminished pressure, dilute hydrochloric acid was added and the solution extracted with ether. The ether layer was extracted with a saturated sodium bicarbonate solution. The ether layer was dried, concentrated and distilled to yield 4.41 g. (54.3%) of recovered starting material, b.p. 68–74° (0.18 mm.), $n^{25}\text{D}$ 1.4620.

The bicarbonate extract was acidified and extracted with ether to yield 0.2 g. of a liquid forerun boiling at 169° (0.6 mm.) and 0.9 g. of an acid which crystallized in the condenser. A single recrystallization from a mixture of chloroform and petroleum ether gave colorless crystals of (+)-α-methylglutaric acid (VI), m.p. 82–83°, $[\alpha]^{27}\text{D}$ +24.2° (*c* 2.18, $CHCl_3$) and $[\alpha]^{27}\text{D}$ +20.6° (*c* 2.49, 95% ethanol), which showed no depression in melting point on admixture with VI obtained from the degradation of nepetonic acid (II). Based on the weight of XVIII which was consumed the yield of VI was 39%.

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[24] The hydrogen peroxide used in this procedure was first assayed iodometrically according to the method of I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," Third Ed., The Macmillan Co., New York, N. Y., 1952, p. 600. Hydrogen peroxide of low concentration was found to give incomplete oxidation.

[25] In the present work it was found necessary to introduce this step in order to obtain pure nepetonic acid since nepetalinic acid (XII), m.p. 85°, co-distils with nepetonic acid as a mixture of acids and nepetalinic anhydride.

[26] O. L. Brady, *J. Chem. Soc.*, 756 (1931).