[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY, THE STATE UNIVERSITY OF NEW JERSEY]

The Stereochemistry of 4a-Methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene

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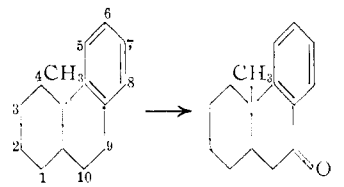
The configurations of the *cis* and *trans* forms of 4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene have been established by degradation to the known isomers of 2-methyl-2-carboxycyclohexaneacetic acid. Definite proof was obtained in this way that the major product from the sulfuric acid cyclization of 1-β-phenylethyl-2-methylcyclohexanol was the *cis* isomer. A minor product, previously believed to be a spirane, now has been proved to be the *trans* isomer; therefore this particular cyclization is not wholly stereospecific with a ratio of *cis* to *trans* forms of approximately four to one.

In a previous publication[2] it was reported that the major product resulting from the cyclization of 1-β-phenylethyl-2-methyl-1-cyclohexanol was one of the isomers of 4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (Ia). On the basis of a mechanism for the cyclization of β-arylethylcyclohexanols which has been proposed,[3] this isomer was assigned the *cis* configuration. The purpose of this research was to establish definitely whether or not this cyclization product was actually the *cis* isomer.

The first step in achieving this goal was the preparation of 9-keto-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (II).



Ia,b IIa,b

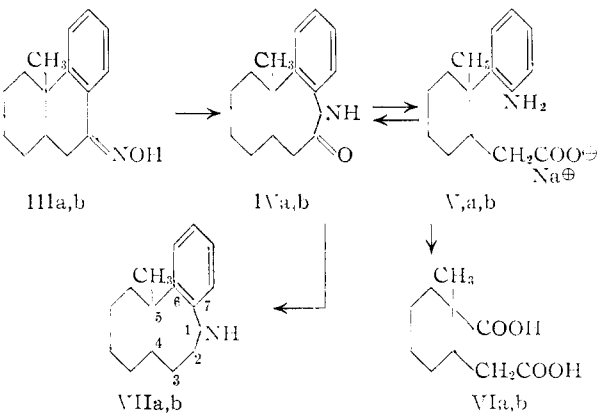
When distilled, but unfractionated, hydrocarbon I was used for the oxidation to ketone II, there resulted rather unexpectedly a mixture of two ketones. These ketones were separated by fractional crystallization of their oximes and then identified as the *cis* and *trans* forms of II by conversion of the oximes to the known 2,4-dinitrophenylhydrazones.[2,4]

The product from a previous cyclization,[2] obtained in 85% yield, had been fractionated carefully to yield 7% of uncyclized olefin, 71% of pure *cis* isomer and 22% of material having a slightly higher refractive index than the major product. When this experiment was carried out it was thought that this latter material was a mixture of the *cis* isomer and a spirane. The basis for this belief was the observation that fractional distillation was successful for the separation of a spirane from the isomeric 1,2,3,4,4a,9,10,10a-octahydrophenanthrenes[5] while the *cis* and *trans* forms of this octahydrophenanthrene were reported to be inseparable by distillation.[6] We now have proved that the fraction with the high refractive index was actually a mixture containing both isomers of I.

Thus the *trans* isomer was present not only in the cyclization product obtained in the present work but also in the product previously reported.[2]

The amount of *trans* isomer from the cyclization with 85% sulfuric acid[2] must be less than 20% since 76% of the total cyclized product was the pure *cis* isomer and the remaining 24% was a mixture of both isomers. The cyclization with 90% sulfuric acid yielded more of the *trans* isomer[7]; an increase in the amount of *trans* isomer under more drastic cyclization conditions is in accord with the theoretical prediction.[3]

The structure proof plan next required that the oximes IIIa,b of ketones II be carried through a Beckmann rearrangement. Polyphosphoric acid[8]



IIIa,b IVa,b Va,b

VIIa,b VIa,b

proved to be very effective for this purpose. The ultraviolet and infrared spectra of the lactams IVa,b indicated that this rearrangement had proceeded in the desired fashion, yielding a product with the nitrogen atom linked directly to the aromatic nucleus.

The hydrolysis of the lactams failed completely in acid solution and was successful in basic solution only when the temperature was raised to 200°. When the sodium salts resulting from the hydrolysis were acidified, the lactams were regenerated immediately even at room temperature. It was surprising that a seven-membered lactam ring should be formed so readily.

Before the hydrolysis conditions were worked out an alternate possibility was explored by converting the lactams to the corresponding amines which might be oxidized to acids VIa,b.

(1) Abstracted from a thesis presented by M. T. Beachem to the Graduate School for the Ph.D. Degree, June, 1954.

(2) R. A. Barnes and R. T. Gottesman, THIS JOURNAL, **74**, 35 (1952).

(3) R. A. Barnes, *ibid.*, **75**, 3004 (1953).

(4) R. A. Barnes and M. D. Konort, *ibid.*, **75**, 303 (1953).

(5) D. Perlman, D. Davidson and M. T. Bogert, *J. Org. Chem.*, **1**, 288, 300 (1936).

(6) J. W. Cook, C. L. Hewett and A. M. Robinson, *J. Chem. Soc.*, 168 (1939).

(7) From the yields of *cis*- and *trans*-oximes isolated, it may be estimated that as much as 40% of *trans* isomer was formed. This estimate is reliable if no fractionation of the isomers occurs during the oxidation to the ketones nor in the conversion of the ketones to the oximes.

(8) E. C. Horning, THIS JOURNAL, **74**, 2680, 5123 (1952).

The first attempts to oxidize the salts Va,b with potassium permanganate were unsuccessful. A study of the stability of a synthetic sample of VIa toward oxidation resulted in the selection of experimental conditions which would permit the oxidation to take place without complete destruction of the desired acids. In this way yields of 15–17% of crystalline oxidation products were isolated. The identification of these products with synthetic samples of the isomeric acids VI by melting point determinations and by comparison of infrared spectra, definitely proved that hydrocarbon Ia was the *cis* isomer and Ib the *trans* isomer.

This proof would not be unequivocal if there were any doubt concerning the structures of acids VIa,b. The authentic samples of the two acids were prepared by the procedures of Bachmann and Kushner,[9] who related them to the next lower homologs, the 1-methylcyclohexane-1,2-dicarboxylic acids. The structural assignments in this latter series depend on the fact that there is only a single anhydride which must certainly have the *cis* structure.

Experimental[10]

4a-Methyl-9-keto-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (II).—4a-Methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (I) was prepared in 79% yield by cyclization of 1-β-phenylethyl-2-methylcyclohexanol[2] using 90% sulfuric acid at 5°. This product was distilled, b.p. 118–120° (1 mm.), using a 15-in. column packed with glass helices, $n^{25}D$ 1.5505 (pure *cis* isomer[2] of I had $n^{25}D$ 1.5500). The purpose of this distillation was only to remove low boiling impurities; a much more efficient column, operated at a high reflux ratio is necessary for separation of the isomers of I.[2]

Hydrocarbon I (90 g.) purified in this way, was dissolved in acetic acid (855 ml.) and treated with a solution of chromium trioxide (103.5 g.) in 80% acetic acid (194 ml.) at 10–15°. After ten hours at this temperature the reaction mixture was allowed to stand for 3 days at room temperature. The solution was diluted with water and the product extracted with benzene. The crude ketone was distilled twice using the 15-in. column and finally there was obtained 45 g. (47%) of II which boiled at 122–130° (0.48 mm.), $n^{25}D$ 1.5667. This product had $\lambda_{max}^{95\%\ EtOH}$ 251 mμ (ε 10,850) and 293 mμ (ε 4,750).

Oximes IIIa,b of Ketone II.—A mixture of hydroxylamine hydrochloride (12.8 g.) sodium bicarbonate (15.5 g.) and water (50 ml.) was swirled until the reaction was complete, then ketone II (39 g.) and glacial acetic acid (5 ml.) were added followed by sufficient ethanol (*ca.* 300 ml.) to produce a clear solution. This solution was warmed on the steam-bath for 3 hours and then allowed to stand overnight. The crystalline precipitate (28.5 g., m.p. 117–145°) was collected and the filtrate concentrated twice to yield additional crystalline material (10.8 g., m.p. 116–160° and 122–124°).

The first precipitate was slurried with boiling 95% ethanol (50 ml.) and the insoluble material (13 g.) filtered. This was found to be mainly one isomer (*trans*), m.p. 162–166°; further recrystallization from ethanol raised the melting point to 177–178°.

Anal. Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35; N, 6.10. Found: C, 78.72; H, 8.17; N, 6.36.

Evaporation of the filtrate from the hot alcohol separation left a residue (11.1 g., m.p. 126–129°) which was largely the second isomer (*cis*). Recrystallization from benzene raised the melting point to 139–140°.

Anal. Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35; N, 6.10. Found: C, 78.77; H, 8.32; N, 6.03.

The second crop of crystals (10.8 g.) from the preparation of the oxime were also largely this isomer; thus the amount of *cis*-III originally formed is estimated to have been 23 g. and the amount of *trans*-III 15 g.

The ultraviolet spectra of the two oximes were almost identical, $\lambda_{max}^{95\%\ EtOH}$ 253 mμ (ε 12,000).

Hydrocarbon I, previously prepared,[12] had been carefully fractionated to yield 14 fractions (the first four fractions were combined and refractionated to yield eight fractions for a total of 18 previously mentioned). Fraction 12 (b.p. 119° (1.0 mm.), $n^{25}D$ 1.5503) and fraction 14 (b.p. 119.5° (1.0 mm.), $n^{25}D$ 1.5008) from the original fractionation were combined (31.7 g.) and oxidized with chromic acid to ketone II which was converted directly to the oxime. Recrystallization of the crude oxime (12.6 g.) yielded *cis*-III (3.7 g.) and *trans*-III (7.3 g.).

The *cis*-oxime (0.5 g.) in ethanol (40 ml.) was treated with a solution of 2,4-dinitrophenylhydrazine (2.16 g.) in sulfuric acid (10.8 ml.), water (15 ml.) and ethanol (15 ml.). The mixture was refluxed for 15 minutes and the product filtered and washed free of acid. This 2,4-dinitrophenylhydrazone melted at 184.2–184.5°. The melting point of a mixture of this sample and the 2,4-dinitrophenylhydrazone previously prepared[2] (m.p. 182.5–184°) from hydrocarbon Ia melted at 183.4–184.2°.

The *trans*-oxime by similar procedure process, was converted to a 2,4-dinitrophenylhydrazone which melted at 210–211° after recrystallization from ethanol–ethyl acetate. The melting point of a mixture of this sample and the derivative (m.p. 209.5–210.5°) prepared from hydrocarbon Ib[4] melted at 209–210°.

2-Keto-5-methyl-4,5-cyclohexano-2,3,4,5-tetrahydro-6,7-benzazepine-1 (IV). *cis* Isomer.—A mixture of the *cis*-oxime (0.50 g.) and polyphosphoric acid (15 g.) was heated at 130° for 10 minutes.[8] Water was added carefully to the reaction mixture and the product extracted with ethyl acetate. There was obtained 0.30 g. (60%) of product which melted at *ca.* 133°. Recrystallization from ethyl acetate raised the melting point to 152–153°; $\lambda_{max}^{95\%\ EtOH}$ 246 mμ (ε 12,500),[11] $\lambda_{max}^{CHCl_3}$ 2.95 μ (NH group).[12]

Anal. Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35; N, 6.10. Found: C, 78.86; H, 8.27; N, 6.15.

***trans* Isomer.**—This substance was obtained in 92% yield (m.p. 160–165°) from *trans*-oxime III (0.5 g.) by the same procedure[8] as for the other isomer. After alternate recrystallization from ethyl acetate and ligroin this lactam melted at 174–175°, $\lambda_{max}^{95\%\ EtOH}$ 244 mμ (ε 12,570), $\lambda_{max}^{CHCl_3}$ 2.94 μ (NH) and 5.98 μ (carbonyl).

Anal. Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35; N, 6.10. Found: C, 78.72; H, 8.17; N, 6.36.

5-Methyl-4,5-cyclohexano-2,3,4,5-tetrahydro-6,7-benzazepine-1 (VII). *cis* Isomer.—A solution of *cis*-lactam IV (1.0 g.) in anhydrous ether (50 ml.) was treated with a 1 *M* solution of lithium aluminum hydride (70 ml.). The reaction mixture was stirred at room temperature for 15 hours and then refluxed for one hour. The reaction mixture was decomposed with wet ether, the inorganic material filtered off and the ether solution dried and concentrated to 20 ml. The addition of a solution of picric acid (1.0 g.) in ether (80 ml.) caused the precipitation of the picrate of VIIa. There was obtained 1.55 g. (77%) of yellow crystals which melted at 170–172.5°, after recrystallization from ethanol.

Anal. Calcd. for $C_{21}H_{24}O_7N_4$: C, 56.74; H, 5.44; N, 12.60. Found: C, 57.24; H, 5.63; N, 12.47.

***trans* Isomer.**—By the same procedure *trans*-lactam IV (1.0 g.) yielded 1.80 g. (90%) of picrate which melted at 158–160° after recrystallization from ethanol.

Anal. Calcd. for $C_{21}H_{24}O_7N_4$: C, 56.74; H, 5.44; N, 12.60. Found: C, 56.95; H, 5.40; N, 12.42.

Nitration of Lactams IVa,b.—*cis*-Lactam IV (1 g.) was dissolved in concentrated sulfuric acid (5 ml.) and this

(9) W. E. Bachmann and S. Kushner, THIS JOURNAL, **65**, 1963 (1943).

(10) All melting points were determined on the Kofler hot-stage. The microanalyses were by the Microanalytical Laboratory of Merck and Co., Inc., Rahway, N. J.; this assistance the authors gratefully acknowledge.

(11) F. W. Klingstedt, *Z. physik. Chem., Abt. B*, **1**, 74 (1928), has reported that acetanilide has λ_{max}^{EtOH} 240 mμ; if the oxime had rearranged in the other possible way the ultraviolet spectrum would have been similar to that of benzamide, λ_{max}^{EtOH} 285 mμ as reported by T. Guilmart, *Bull. soc. chim.*, [5] **5**, 1209 (1938).

(12) R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1248 (1947), have reported for dilute solutions of a monosubstituted amide an NH stretching frequency at 2.91μ; this is shifted to 2.94 for compounds with a phenyl group on the nitrogen atom.

solution was maintained at 5° while a mixture of sulfuric acid (5 ml.) and concd. nitric acid (5 ml.) was added dropwise. When the addition was complete, the solution was poured into water, the precipitate filtered and washed free of acid. There was obtained 1.1 g. (92%), m.p. 185–190°, of a mononitro derivative[13] which melted at 208–209° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{15}H_{18}O_3N_2$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.32; H, 6.62; N, 10.63.

By this same procedure *trans*-lactam IV (1 g.) yielded 1.0 g. (90%) of a nitration product, m.p. 230–240°, which melted at 241–243° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{15}H_{18}O_3N_2$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.58; H, 6.36; N, 10.66.

***cis*-2-Methyl-2-carboxycyclohexanacetic Acid.**—*cis*-Lactam IV a (5 g.) was heated at 200° with 2.5 *N* sodium hydroxide solution (200 ml.) in a glass-lined autoclave for 15 hours. The cold hydrolysis solution was extracted with ether to yield 2.7 g. (54%) of unhydrolyzed lactam.

The lactams also can be hydrolyzed by refluxing for 15 hours with potassium hydroxide in ethylene glycol. The salts could not be separated efficiently from the ethylene glycol which interfered with the oxidation step. Acidification of the basic solution immediately regenerated the lactams even at room temperature.

The first oxidation carried out by refluxing the salts with potassium permanganate solution for one hour yielded none of the desired acidic products. A synthetic sample of *cis*-acid VIa was 68% destroyed under these conditions. However, when this acid was stirred with basic permanganate solution at room temperature for 12 hours, 77% was recovered unchanged

The basic hydrolysis solution, after removal of unchanged lactam, was diluted to a total volume of 250 ml. and a 50-ml. aliquot, which contained 0.002 mole of the sodium salt Va, was treated with potassium permanganate (2.73 g.) in water (50 ml.) at room temperature for one hour. The solution was acidified carefully with 4 *N* hydrochloric acid (50 ml.) and the solution stirred for an additional hour before excess sodium bisulfite solution was added to stop the reaction.

The organic products were extracted with ethyl acetate (300 ml.) and the ethyl acetate solution concentrated to 50 ml. and extracted with 5% sodium bicarbonate solution (150 ml.). Acidification of the sodium bicarbonate extract followed by extraction with ethyl acetate and evaporation of this solvent yielded an oil. The pure acid was obtained by dissolving the oil in petroleum ether–acetone (5:3 parts by volume) and passing this solution through a column of silica gel. The effluent from the column yielded 95 mg. of a crystalline fraction containing some oil. Recrystallization of this fraction from ethyl acetate yielded 66 mg. (15%) of acid which melted at 163.5–164.5°.

Anal. calcd. for $C_{10}H_{16}O_5$: C, 59.98; H, 8.05. Found: C, 60.21; H, 7.97.

The melting point of a mixture of this acid with an authentic sample of the *cis* isomer prepared by the procedure of Bachmann and Kushner[9] was 164–165°; the infrared spectra of the two samples were identical. Also, the infrared spectrum of the crude oily oxidation product indicated the presence of only the *cis* isomer of acid VI.

***trans*-2-Methyl-2-carboxycyclohexaneacetic Acid.**—When the hydrolysis of *trans* lactam IV (5 g.) was carried out as for the *cis* isomer only 0.5 g. (10%) of unhydrolyzed lactam was recovered. The oxidation was carried out as previously described to yield, from an aliquot (containing 0.002 mole) of the hydrolysis solution, an oily acid which crystallized on trituration with petroleum ether. The crystalline product, 71 mg. (17%), melted at 165–175° but after the recrystallization from ethyl acetate the melting point was 174–178°.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 59.98; H, 8.05. Found: C, 59.89; H, 7.86.

The melting point of a mixture of this sample with an authentic sample of the *trans* isomer of VI prepared by the method of Bachmann and Kushner[9] was 176–178°. The infrared spectra of the two samples were identical.

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(13) The nitro group probably entered the ring *para* to the acylamino group, to yield 2-keto-5-methyl-7-nitro-4,5-cyclohexano-6,7-benzazepine-1.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY, AND THE LABORATORIES OF THE MEMPHIS CHEMICAL COMPANY, CAIRO]

Furo-chromones and -Coumarins. XII. Synthesis of Fraxinol from Bergapten and of Baicalein from Visnagin

BY ALEXANDER SCHÖNBERG, NASRY BADRAN AND NICOLAS A. STARKOWSKY

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The syntheses of fraxinol (IV) from bergapten (I) by a 3-step procedure and of baicalein (XIII) from visnagin (VII) by a 6-step procedure are given, the latter comprising three successive oxidation reactions, using selenium dioxide, chromic acid and hydrogen peroxide.

Bergapten (I) and visnagin (VII), which can be extracted together with the medically important xanthotoxin and khellin from the Egyptian plants *Ammi majus* (L.) and *Ammi visnaga* (L.), respectively, have now been used as starting materials in the synthesis of other products, namely, of some coumarins of the fraxinol group and some flavones of the baicalein group. In these syntheses, the key reaction was the easy oxidation of the furan ring of visnagin (VII)[1a] and bergapten (I)[1b] with chromic acid. This oxidation, which leads to derivatives of salicylaldehyde, now has been extended also to a furoflavone (X) prepared from visnagin.

Synthesis of Fraxinol (IV).—The methylation of apoxanthoxyletin (II), obtained by the oxidation of bergapten (I),[1b] with methyl iodide and potassium carbonate in acetone, led to 5,7-dimethoxy-6-formylcoumarin (III). Replacement of the formyl group by a hydroxyl group by means of oxidation with hydrogen peroxide in sulfuric acid medium afforded 5,7-dimethoxy-6-hydroxycoumarin (fraxinol) (IV) in good yield. This substance has been synthesized previously on different lines.[2,3]

The oxidation of apoxanthoxyletin (II) itself with alkaline hydrogen peroxide led to 6,7-dihydroxy-5-methoxycoumarin (V), which has then been methylated to 5,6,7-trimethoxycoumarin (VI).

(1) (a) A. Schönberg, N. Badrau and N. A. Starkowsky, THIS JOURNAL, **75**, 4992 (1953); (b) **77**, 1019 (1955).

(2) E. Späth and Z. Jerzmanowska-Sienkiewiczowa, *Ber.*, **70**, 698 (1937).

(3) V. J. Dalvi, R. B. Desai and S. Sethna, *J. Indian Chem. Soc.*, **28**, 366 (1951).