6.6 g. (90%) of pale yellow, viscous oil, b.p. 156° (1.5 mm.), which rapidly solidified to a mass of colorless needles, m.p. 60°, λ_{max} 231 mμ in 95% ethanol (ε 29,250).

Anal. Calcd. for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.19; H, 11.29; N, 6.27.

Reaction of All-*trans*-II with Maleic Anhydride.—All-*trans*-II (100 mg.), maleic anhydride (40 mg.) and benzene (0.8 ml.) were sealed under nitrogen and heated at 100° for 17 hours. On cooling to 5°, a viscous yellow oil separated which could not be induced to crystallize. Evaporation of the benzene gave only a resin.

All-*trans*-II (1 g.), heated at 100° with 0.75 g. of maleic anhydride for 1 minute and then cooled, gave a viscous, orange oil. This was digested with ether (an orange resin remained insoluble); the ether-soluble extractive was a viscous, yellow oil which would not crystallize.

Hydrogenation of All-*trans*-II.—An ethanol solution of 0.2064 g. of all-*trans*-II was hydrogenated with 50 mg. of reduced platinum oxide catalyst. In 15 minutes 42.8 ml. (cor.) of hydrogen was taken up and the reaction then ceased. (The theoretical requirement for 2 moles of hydrogen for this weight of a substance of molecular weight 223 is 41.5 ml.) The reaction mixture was separated from the catalyst, and the solvent was removed at reduced pressure, leaving 210 mg. of a colorless oil which crystallized in rosettes of needles, m.p. 37.5–38.0°, identical with N-isobutylcapramide, m.p. and mixed melting point 37.5–38.0°.

Oxidation of All-*trans*-II.—One gram of all-*trans*-II suspended in 100 ml. of water maintained at 50–60° was treated, with stirring, with 3.8 g. of finely powdered potassium permanganate added in small portions. When the reaction mixture had become colorless, the manganese dioxide was filtered off and washed thoroughly with warm water. The combined aqueous filtrates were concentrated down to 10 ml. and made acid to congo red with sulfuric acid. The solution was steam distilled to remove the volatile acids and then extracted with ether for 4 days in a continuous extractor. The ether solution was freed of solvent, and the residue was taken up in chloroform and kept at 0° overnight. The crystals which separated were subjected to sublimation in a microsublimator, yielding 277 mg. (70%) of colorless solid, which sublimed at 100–105° (15 mm.) and melted at 185–186° dec. It rapidly reduced an aqueous solution of potassium permanganate, and was identified as anhydrous oxalic acid by a mixed melting point determination with an authentic specimen (m.p. 186–187° dec.).

The chloroform solution was evaporated to dryness and the yellowish solid residue was recrystallized from benzene, giving 564 mg. (74%) of feathery needles, m.p. 92.0–92.5°, which were very soluble in water.

Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.08. Found: C, 55.42; H, 8.51; N, 8.15.

The product was identical with N-isobutylsuccinamic acid, m.p. 92.0–92.5°, by mixed melting point with an authentic specimen prepared by the following procedure. A refluxing mixture of 54 g. of succinic anhydride and 200 ml. of anhydrous ether was treated dropwise with 41 g. of isobutylamine; lumps of white solid which gradually formed were broken up from time to time. The mixture was refluxed for 2 days, cooled, and filtered, and the oily solid was recrystallized thrice from benzene to give 62.1 g. (65%) of long, feathery needles, m.p. 92.0–92.5°.

The solution of steam-volatile acids obtained above was neutralized with sodium hydroxide solution, concentrated to a small volume on the steam-bath, and acidified to congo red with sulfuric acid. The solution was rapidly steam distilled until all material acid to congo red had distilled over. The distillate was neutralized with dilute sodium hydroxide solution, the neutral solution was evaporated to dryness, and the *p*-phenylphenacyl ester was prepared. It melted at 82° and a mixed melting point determination with authentic *p*-phenylphenacyl butyrate, m.p. 82°, showed no depression.

The distilland above was neutralized with sodium hydroxide solution, concentrated to a very small volume on the steam-bath, acidified to congo red with sulfuric acid, and extracted with ether in a continuous extractor for 3 days. The ether solution was dried and freed of solvent, yielding an additional 15 mg. of N-isobutylsuccinamic acid.

Examination of *Spilanthes americana* Flower Heads.—The finely ground flower heads (962 g.) were extracted in a soxhlet extractor overnight with petroleum ether (b.p. 30–40°). The extract was concentrated to 250 ml. and extracted with three 75-ml. portions of nitromethane. The combined nitromethane solution was freed of solvent under reduced pressure, the residue was taken up in ethyl ether, and the ether solution was washed with water, 5% hydrochloric acid solution, 5% sodium hydroxide solution and water, and dried over sodium sulfate. Removal of solvent under reduced pressure left 10 mg. of a yellow oil which could not be induced to crystallize. It was very weakly pungent and, although showing some knockdown when tested against adult house flies,[15] it caused no mortality of these insects.

BELTSVILLE, MARYLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF CORNELL UNIVERSITY]

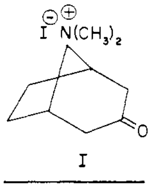
Elimination Reactions of Bicyclic Quaternary Salts. II. The Base Degradation of Pseudopelletierine Methiodide

BY J. MEINWALD AND S. L. EMERMAN

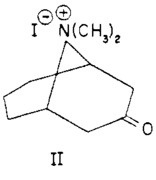
RECEIVED APRIL 9, 1956

The base degradation product of pseudopelletierine methiodide (II) is shown to be a *mixture* of acetophenone and 1-cyclohexenyl methyl ketone rather than a dihydroacetophenone as previously considered. In explanation of these results, a reaction sequence involving (1) formation of a cycloöctadienone III, (2) conversion of this intermediate into a cyclohexadienyl methyl ketone IX, and (3) a hydrogen exchange reaction, is suggested and discussed in detail.

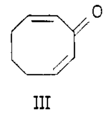
The claim that tropinone methiodide (I) is transformed by a variety of bases into dimethylamine and a dihydrobenzaldehyde has recently been discredited,[1] and it is now clear that no rearrangement accompanies this elimination reaction. We have now reinvestigated the behavior of the closely related alkaloid derivative pseudopelletierine methiodide (II), which has been reported to undergo a ring contraction on treatment with strong base, giving rise to dimethylamine and a *dihydroacetophenone*.[2] The results of these studies provide the subject of the present communication.



I



II



III

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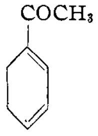
[1] J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, THIS JOURNAL, **77**, 4401 (1955).

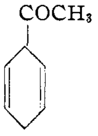
[2] G. Ciamician and P. Silber, *Ber.*, **25**, 1601 (1892); *Gazz. chim. ital.*, **22** (II), 514 (1892); *Ber.*, **26**, 156 (1893).

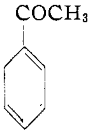
In agreement with the previous report, a liquid product giving analytical figures in accord with the composition $C_8H_{10}O$ was obtained (in 43% yield) by steam distillation of a suspension of pseudopelletierine methiodide in aqueous barium hydroxide. The degradation procedure was modeled after that described in the literature,[2] and there is no reason to doubt that the liquid obtained corresponds to that previously designated as dihydroacetophenone.

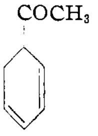
Our first expectation, based on the tropinone analogy and on the principle of minimum structural change,[3] was that the presumed dihydroacetophenone would prove to be a cycloöctadienone, such as III. To distinguish between unrearranged and rearranged structures, the degradation product was subjected to catalytic hydrogenation in the hope of obtaining either cycloöctanone or cyclohexyl methyl ketone. The hydrogenation took place with surprising difficulty, proceeding first at a normal rate, but requiring acid catalysis for the complete introduction of two molar equivalents of hydrogen. The reduced material, a ketone, gave a semicarbazone which strongly depressed the melting point of authentic cycloöctanone semicarbazone. That the hydrogenated product was in fact cyclohexyl methyl ketone (IV) was demonstrated by direct comparison of a distilled sample with a synthetic specimen of IV and by comparison of two pairs of crystalline derivatives. This evidence led unavoidably to the conclusion that the degradation product actually contained a six-membered ring.

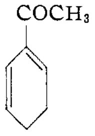
At this point it seemed convincing that the early work in this field merited serious consideration, and experiments were planned to determine which of the five possible dihydroacetophenones (V–IX) might be present in the pseudopelletierine methiodide degradation product.


V

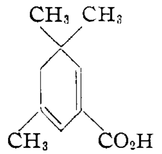

VI

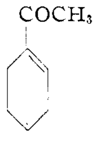

VII


VIII


IX

A carefully distilled (b.p. 51–52° (2.4 mm.)), colorless sample of the liquid showed a single ultraviolet absorption maximum at 240 mμ, log ε 4.07. This spectrum excludes V (λ_{max} 302 mμ, log ε 3.85[4]), VI (no possible intense absorption beyond 210 mμ) and VII (λ_{max} 245 mμ, log ε 3.70[5,6]) from further consideration. Since 1,3-cyclohexadiene itself shows λ_{max} 256 mμ, log ε 3.90,[7] structure VIII, with the same chromophore, is unsatisfactory.[8] On the basis of a report that the diene acid X shows λ_{max} 264[9,10] mμ, it seems allowable to estimate that a compound with structure IX would show maximal absorption in the region between 260 and 280 mμ. It therefore appeared that although the hydrogenation evidence supported the contention that pseudopelletierine methiodide had been transformed into a dihydroacetophenone, no dihydroacetophenone structure could be written which was compatible with the ultraviolet absorption data.


X


XI

All structural hypotheses having been exhausted at this point, further exploratory work was carried out. Thus, continued examination of the ketonic product led to the following observations: (1) No adduct was formed with maleic anhydride or N-phenylmaleimide. (2) Alkaline sodium hypoiodite oxidation yielded iodoform and benzoic acid. (3) A Kuhn–Roth determination indicated the presence of one C-methyl group. (4) Treatment with chloroanil, under conditions known to bring about aromatization of VII,[5] led to the recovery of unchanged starting material. (5) Sodium borohydride reduction gave a product with no intense ultraviolet maximum beyond 210 mμ. (6) Both ozonolysis and potassium permanganate oxidation gave adipic acid.

It was clear from a perusal of these results that *no single structure* could be responsible for this pattern of behavior. The simplest explanation was that the substance $C_8H_{10}O$ was actually a *mixture* of acetophenone and 1-cyclohexenyl methyl ketone (XI), with an average composition corresponding to that of a dihydroacetophenone. The validity of this conjecture was readily established. An authentic equimolar mixture of these two components was prepared, and was found to have ultraviolet and infrared spectra in excellent agreement with those of the pseudopelletierine degradation product. Finally, the 2,4-dinitrophenylhydrazone of the degradation product was chromatographically resolved into its two easily recognized constituents.

Discussion of Mechanism.—The failure of our "theoretical" considerations to predict, as well as the failure of earlier workers to discover the nature of the pseudopelletierine methiodide degradation product is apparent. Rationalizing the transformation after the fact is a less demanding, although not uninteresting task. Considering the process of ring contraction first, the following series of steps (equation 1) seems highly plausible. The key features, involving a retrograde aldol condensation and subsequent aldol cyclization in a new direction, find analogy in the facile transformation

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(3) G. W. Wheland, "Advanced Organic Chemistry," 2nd Edn., John Wiley and Sons, Inc., New York, N. Y., 1949, p. 95.

(4) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).

(5) K. Bowden and E. R. H. Jones, *ibid.*, 52 (1946).

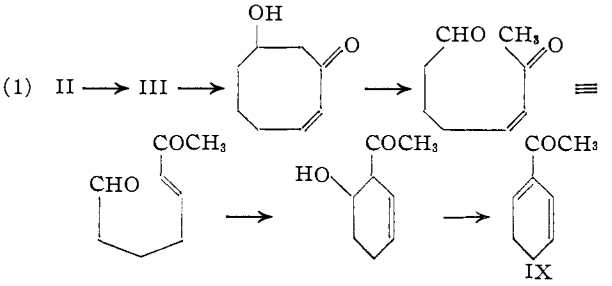
(6) The non-identity of the dienone VII and the pseudopelletierine degradation product was confirmed by direct infrared comparison of the two materials. An authentic sample of VII was prepared by a route slightly different from that previously described in the literature (see S. L. Emerman and J. Meinwald, *J. Org. Chem.*, **21**, 375 (1956)).

(7) V. Henri and L. W. Pickett, *J. Chem. Phys.*, **7**, 439 (1939).

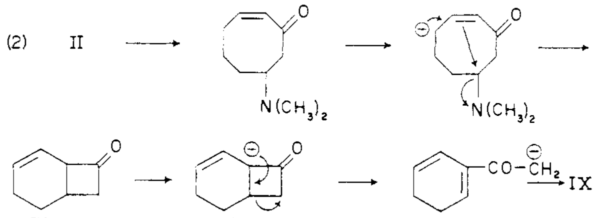
(8) This conclusion is based on the assumption that the spectrum of VIII would be free of transannular effects (*cf.* ref. 1). Other evidence which excludes VIII on more rigorous grounds is presented in the sequel.

(9) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 607 (1954).

(10) We are grateful to Dr. Braude for supplying us with confirmatory evidence on the structure of X in a private communication. The possibility that our degradation product might be 1-cyclohexenyl methyl ketone, suggested to us by Dr. Braude on the basis of ultraviolet spectra, was precluded by the elementary analyses, as well as by comparison of other properties of the two substances.

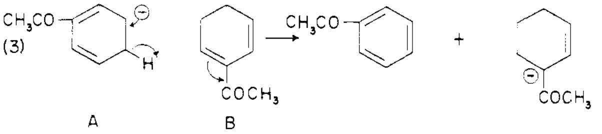


of 2-methyl-1-cyclohexenecarboxaldehyde to 1-cyclohexenyl methyl ketone.[11] An alternate sequence, which would yield the same product *via* a transannular displacement (equation 2), may also be envisioned. Although attention has been called to this type of mechanism in the case of the degradation of homopseudopelletierine methiodide,[12] it is considered to be somewhat less likely in the present case because of the strain that would be involved in generating the [4,2,0]bicyclooctene system.



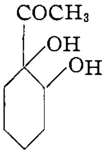
Since we have already proved that the actual degradation product is not IX, some explanation of the formation of acetophenone and 1-cyclohexenyl methyl ketone from this postulated intermediate is required. These products might be expected on the basis of purely thermodynamic considerations, but a plausible path for the apparent disproportionation should be discernible.

One attractive hypothesis, involving donation of a single hydrogen nucleus with its pair of electrons from the enolate anion of IX to a neutral molecule of IX, producing acetophenone and the enolate anion of XI is represented below in equation 3. The transition state would be stabilized by the incipient aromaticity of the hydride donor, A. Furthermore, the strong base required for the initial elimination of the nitrogen bridge would serve to generate the anion A from IX.[13]

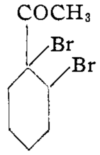


It may be noted that the difference in the course of the degradation of the seven-membered ring alkaloid I and the eight-membered ring analog II is readily explicable. The steps of reverse aldolization and cyclization, when applied to a cycloheptadienone derived from I, would give rise to a cyclopentadienyl methyl ketone. One might anticipate difficulty in a ring-closure step leading to this product. Furthermore, it is unlikely that a cyclopentadienyl ketone of this type would be sufficiently stable to permit isolation from a hot, alkaline medium.

Experiments have been carried out in the hope of independently preparing the postulated reaction intermediates III and IX. These ends have not yet been achieved. Stepwise degradations of either II or the corresponding alcohol have proven impracticable. The diol XII and dibromide XIII have been prepared, but conditions for their transformation into the desired dienone have yet to be developed.



XII



XIII

If the reaction paths discussed in connection with this degradation are valid, there is the distinct possibility that many dihydroaromatic systems (analogous to IX) capable of forming enolate anions may be found to act as hydride ion donors. We are now examining the behavior of some authentic dihydroacetophenones and related compounds, and hope to present the results of these studies in a subsequent publication.

Acknowledgment.—We are most grateful to the Research Corporation for providing partial support for this investigation. We should also like to acknowledge herewith the enthusiastic experimental effort devoted to the early phases of this research by Mr. Jacob Grossman. Finally, we should like to thank Professor A. C. Cope of the Massachusetts Institute of Technology for his generosity in donating the pseudopelletierine used in our initial experiments.

Experimental[14]

Pseudopelletierine Methiodide (II).—Equimolar amounts of glutaraldehyde,[15] acetonedicarboxylic acid and methylamine hydrochloride in a phosphate buffer at *p*H 3–5 were converted to pseudopelletierine in 50–60% yield.[16] Crystalline II was obtained on treatment of the crude alkaloid with methyl iodide in ethanol.

Degradation of II in Concentrated Barium Hydroxide Solution.—Barium hydroxide (45 g.) was dissolved in 450 ml. of boiling water, pseudopelletierine methiodide (7.0 g.) was added and the solution steam distilled for 30 minutes. The combined distillate from four similar runs was extracted with ether. After drying over magnesium sulfate,

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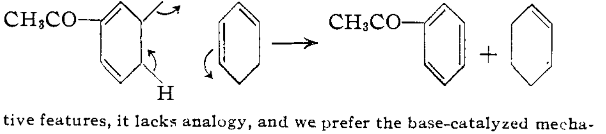
[11] A. S. Dreiding and A. J. Tomasewski, THIS JOURNAL, **76**, 6391 (1954). For another possible analogy, see W. G. Dauben and C. W. Vaughan, Jr., *ibid.*, **75**, 4651 (1953).

[12] J. Meinwald and M. Koskenkyla, *Chemistry & Industry*, 476 (1955).

[13] Another possibility which we have considered is a "four-center" type of reaction involving two molecules of IX as shown below. Although a bimolecular hydrogen transfer of this type has some attrac-



tive features, it lacks analogy, and we prefer the base-catalyzed mechanism presented in the preceding paragraph.

[14] All melting points are uncorrected. Analyses are by Mrs. M. Libowitz, Geller Labs., Hackensack, N. J., and Schwarzkopf Microanalytical Lab., Woodside, N. Y. Ultraviolet absorption spectra were recorded in ethanol solution unless otherwise noted.

[15] The aldehyde was initially prepared from its dioxime (ref. 16). Subsequently, a generous gift of aqueous glutaraldehyde was furnished by the Carbide and Carbon Chemicals Co.

[16] A. C. Cope, H. L. Dryden, Jr., C. G. Overberger and A. A. D'Addieco, THIS JOURNAL, **73**, 3416 (1951).

the extract was evaporated down to give 5.0 g. (43%) of a yellow liquid which had an acetophenone-like odor. This sample showed strong bands at 5.92 and 6.00 μ and moderate bands at 6.09, 6.25 and 6.32 μ in the double bond region of the infrared. Distillation through a 30-inch Podbielniak partial reflux column afforded 3.2 g. of a colorless liquid, b.p. 51.3–52.4° (2.4 mm), $n^{20}\text{D}$ 1.5154, $\lambda_{\max}$ 240 mμ, log $\epsilon_{\max}$ 4.07, infrared spectrum identical with that of crude product and significantly different from that of compound VII.[6]

Anal. Calcd. for $C_8H_{10}O$: C, 78.65; H, 8.25; C-methyl, 12.29. Found: C, 78.69; H, 8.02; C-methyl, 12.44.

The distilled product gave a semicarbazone, m.p. 184–186° after two and three recrystallizations from ethanol, $\lambda_{\max}$ 270 mμ, log $\epsilon_{\max}$ 4.27.

Anal. Calcd. for $C_9H_{13}ON_3$: C, 60.31; H, 7.30; N, 23.45. Found: C, 60.15; H, 7.20; N, 23.42.

The recrystallized semicarbazone gave rise to the original degradation product on steam distillation in the presence of phthalic anhydride.

The bright red 2,4-dinitrophenylhydrazone, melting at 205–231° after three recrystallizations from benzene, showed $\lambda_{\max}^{\text{CHCl}_3}$ 380 mμ, log $\epsilon_{\max}$ 4.43. After the degradation product had been identified, this derivative was chromatographed on 1:1 magnesol–Celite to give acetophenone 2,4-dinitrophenylhydrazone (m.p. 241–246°) and 1-cyclohexenyl methyl ketone 2,4-dinitrophenylhydrazone (m.p. 198–203°).

Catalytic Hydrogenation of Degradation Product. A.—To an ethyl acetate suspension of prereduced Adams catalyst in a standard semimicro apparatus was added distilled degradation product (0.33 g., 0.0027 mole). Absorption of hydrogen, initially rapid, became very slow and was stopped after the uptake of 71 ml. Concentrated hydrochloric acid (2 drops) in acetic acid (3 ml.) was introduced, and the hydrogenation allowed to continue to a total uptake of 136 ml. (0.0056 mole). The solution was filtered, washed with aqueous sodium bicarbonate, dried and evaporated to give 0.25 g. of a liquid which differed markedly from cycloöctanone (kindly furnished by Prof. A. T. Blomquist) in the infrared. The semicarbazone, m.p. 171–174°, and cyclooctanone semicarbazone, m.p. 164–168°, showed a mixture melting point of 125–145°.

B.—On a scale of 7.0 g., the degradation product was hydrogenated in a Parr apparatus under acid conditions. The product was isolated as described above. Vacuum distillation through a modified Claisen flask afforded a chief fraction, b.p. 98–100° (20 mm.), $n^{20}\text{D}$ 1.4589, along with lower boiling, ketonic material. The main fraction was nearly identical in infrared spectrum with authentic cyclohexyl methyl ketone, prepared by the action of lithium methyl on cyclohexanecarboxylic acid. It gave a semicarbazone, m.p. 168–171°, and a 2,4-dinitrophenylhydrazone, m.p. 136–138°, which gave no mixture melting point depressions with and showed no spectral differences from the corresponding derivatives of the authentic ketone.

Sodium Hypoiodite Oxidation.—A dioxane–water solution of the degradation product (3.1 g.) was treated with Clorox and potassium iodide, according to the procedure of Adams and Johnson.[17] The acidic product, 0.83 g. of solid after recrystallization from heptane, was purified by two vacuum sublimations and showed m.p. 119–121°. The analytical data, the ultraviolet and infrared spectra, and a mixture melting point showed this compound to be benzoic acid.

Sodium Borohydride Reduction.—An ethanolic solution of the degradation product (6.5 g.) and excess sodium borohydride was allowed to stand overnight at *ca.* 5°. The product, 6.0 g. on isolation in the usual manner, was partially separated on careful distillation into two alcohols. Ultraviolet spectra of the fractions were characterized only by end absorption, log ε 3.5 to 3.8 at 210 mμ. On overnight stirring in the presence of "active" manganese dioxide,[18] these alcohols were reoxidized to ketone samples which differed from the original degradation product and from each other in the relative intensities of the carbonyl bands in the infrared.

A sample of the crude reduction product was hydrogenated to give cyclohexylmethylcarbinol, characterized as its acid phthalate[19] by comparison with an authentic sample.

Ozonolysis.—An ozonide of the degradation product was prepared in methylene chloride at −10° and worked up with 30% hydrogen peroxide. The partly solid residue was recrystallized from acetone–hexane, giving adipic acid (infrared spectrum and mixture melting point), m.p. 145–148°.

Potassium Permanganate Oxidation.—Oxidation of the degradation product by 4% potassium permanganate was found to require strong alkali. Manganese dioxide was removed by reduction with sulfur dioxide, and the product isolated by means of ether extraction. Recrystallization from acetone–hexane and vacuum sublimation afforded adipic acid, m.p. 147–149°.

Quantitative Identification of the Degradation Product.—A mixture of freshly distilled acetophenone (0.2456 g., 0.002044 mole, $n^{20}\text{D}$ 1.5314) and 1-cyclohexenyl methyl ketone[20] (0.2546 g., 0.002048 mole, $n^{20}\text{D}$ 1.4880) showed $n^{20}\text{D}$ 1.5097 and $\lambda_{\max}$ 239 mμ, log $\epsilon_{\max}$ 4.06 (*cf.* $n^{20}\text{D}$ 1.5154 and $\lambda_{\max}$ 240 mμ, log $\epsilon_{\max}$ 4.07 for the distilled degradation product). The infrared spectrum of this artificial mixture was identical with that of the distilled degradation product.

Degradation of II in Less Concentrated Basic Solution.—The methiodide (8.0 g., 0.027 mole) was degraded in 300 ml. of water containing 4.3 g. (0.025 mole) of barium hydroxide by steam distillation. The distillate, worked up as described earlier, gave 0.95 g. of the usual degradation product, a relatively low yield. The distilland was heavily salted and extracted with ether. The dried extracts yielded 0.45 g. of a viscous, orange liquid, showed by infrared spectrum to be pseudopelletierine admixed with a small amount of the usual degradation product. With excess methyl iodide in methanol, this product gave rise to II.

Other experiments using more dilute barium hydroxide and sodium carbonate solutions gave no new products.

Degradations of II in Non-aqueous Media. A.—II was recovered quantitatively after one day in refluxing pyridine–dimethylformamide.

B.—A suspension of II and 1.2 molar equivalents of sodamide in dry, refluxing toluene was stirred at high speed under nitrogen for 45 hours. A gaseous amine was detected in the reflux condenser. Crude II was recovered by filtration. Toluene was distilled from the filtrate, leaving a nonvolatile, gelatinous residue which was not characterized.

C.—II was degraded smoothly in refluxing ethanol containing one molar equivalent of sodium ethoxide. The product, a viscous liquid isolated in roughly 40% yield, exhibited a strong saturated carbonyl band at 5.88 μ in the infrared and a weak ultraviolet maximum at 226 mμ. It could not be successfully characterized.

Hofmann Degradation of Reduced Pseudopelletierine.—Reduction of pseudopelletierine with lithium aluminum hydride in ethereal suspension required nearly a full day under gentle reflux. The product, presumably N-methyl-ψ-granatoline,[21] was converted to the crystalline methiodide (no melting below 350°) in an over-all yield of 89%. Hofmann degradation of the corresponding methohydroxide occurred at 160–360°, giving a viscous oil (55% yield). Treatment with methyl iodide led to the recovery of 20% of this product as the starting methiodide.[22,23] The noncrystalline residue was held in a sealed tube with methyl iodide and methanol at 70° for one day, and the total crude product (after removal of volatile material) subjected to

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[17] R. Adams and J. R. Johnson, "Laboratory Experiments in Organic Chemistry," 4th Edn., Macmillan Co., New York, N. Y., 1949, p. 259.

[18] B. A. Hems, *et al.*, *J. Chem. Soc.*, 1094 (1952).

[19] P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, **75**, 600 (1927).

[20] This ketone was prepared as described by R. E. Christ and R. C. Fuson, THIS JOURNAL, **59**, 893 (1937); complete dehydrochlorination of the initial crude product was carried out by the method of D. Nightingale, E. C. Milberger and A. Tomisek, *J. Org. Chem.*, **13**, 357 (1948).

[21] K. Alder and H. A. Dortmann, *Ber.*, **86**, 1544 (1953), showed that chemical reduction of pseudopelletierine usually gives the ψ-alcohol (hydroxyl oriented *cis* to the nitrogen bridge). These workers report a picrate, m.p. 264–265°, for the ψ-alcohol and a picrate, m.p. 275–276°, for the isomeric alcohol. Our alcohol gives a picrate which decomposes gradually without melting at 260–290°.

[22] R. Willstätter and H. Veraguth, *ibid.*, **38**, 1984 (1905), obtained and fractionally distilled a comparable mixture of Hofmann products.

[23] G. Ciamician and P. Silber, *ibid.*, **26**, 2738 (1893), experienced similar difficulties in degrading this system.

Hofmann degradation. A camphoraceous liquid codistilled with the last traces of water and on isolation was found to contain a band at 6.12 μ but not at 2.9–3.0 μ in the infrared. The new product absorbed nearly two molar equivalents of hydrogen over prereduced Adams catalyst to give cyclooctyl methyl ether, as demonstrated by comparison with an authentic sample.

Cyclooctyl Methyl Ether.—The sodium salt of cyclooctanol, prepared in anhydrous toluene, was refluxed for 13 hours with excess methyl iodide. Filtration of the sodium iodide, followed by fractional distillation, yielded crude cyclooctyl methyl ether, b.p. 185–191.5°, in 63% yield. An analytical sample showed b.p. 185–189°, $n^{21}\text{D}$ 1.4643.

Anal. Calcd. for $C_9H_{18}O$: C, 75.99; H, 12.76. Found: C, 76.27; H, 12.52.

1,2-Epoxycyclohexyl Methyl Ketone.—Compound XI[20] (12.8 g., 0.10 mole) was allowed to stand at room temperature for 12 hours with 33% hydrogen peroxide (20 ml., 0.20 mole) and 4 *N* sodium hydroxide (22 ml.) in 200 ml. of methanol. Dilution of the reactants with one liter of water, followed by sixfold extraction with ether, drying, and removal of the ether, gave a yellowish liquid. Distillation yielded 6.5 g. (45%) of colorless epoxide, b.p. 84–90° (15 mm.), $n^{22}\text{D}$ 1.4633.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.64; H, 8.63. Found: C, 69.08; H, 8.68.

An impure, red 2,4-dinitrophenylhydrazone, $\lambda_{\max}^{\text{CHCl}_3}$ 367 mμ, formed but could not be successfully recrystallized. Attempts to prepare a semicarbazone met with failure.

1,2-Dihydroxycyclohexyl Methyl Ketone (XII).—A suspension of the epoxide (7.0 g.) in 55 ml. of water containing 15 drops of concentrated sulfuric acid was held at steam-bath temperatures for two hours. The mixture was then neutralized with sodium carbonate and extracted with 400 ml. of ether in six portions. Isolation of the product by the usual procedure, followed by distillation, gave 5.3 g. (68%) of colorless XII, b.p. 103.5–105.0° (2.0 mm.), m.p. 53° after recrystallization from ether-pentane.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.85; H, 8.80.

The glycol was partly resinified on exposure to sirupy phosphoric acid for one hour at 100°, and completely resinified on similar treatment at 130°. In the former case, some starting material was recovered.

1,2-Dibromocyclohexyl Methyl Ketone (XIII).—Following a literature procedure, a chilled solution of XI in chloroform reacted with the required amount of bromine, but evaporation of the solvent at low temperatures[24] gave rise to a dark, viscous solution from which no appreciable amount of the desired dibromide could be isolated.

A somewhat more satisfactory procedure involved bromination in acetic acid solution, neutralization of the reaction mixture with aqueous alkali, extraction of the dibromide with ether, decolorizing the ether solution with charcoal, and finally evaporation to dryness. In this way 4.0 g. of XI gave 2.1 g. (23%) of white dibromide, m.p. 43.0–43.5° (lit. value 48°).[24] The dibromide darkened fairly rapidly, even in the absence of light.

Pyridine Treatment of Dibromide XIII.—A sample of XIII (0.30 g.) was refluxed in pyridine (3 ml.) under nitrogen for one hour. Acidification and steam distillation yielded, after the usual work up, 30 mg. (23%) of a liquid very nearly identical in infrared and ultraviolet spectra to an equimolar mixture of acetophenone and 1-cyclohexenyl methyl ketone. Attempts to isolate a diene intermediate were unrewarding.

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[24] R. B. Wagner, THIS JOURNAL, **71**, 3214 (1949).

ITHACA, N. Y.

[CONTRIBUTION OF THE CHEMICAL LABORATORIES OF BRANDEIS UNIVERSITY AND OF SARAH LAWRENCE COLLEGE]

Asymmetry in the Reaction of *l*-Menthol with β-Phenylglutaric Anhydride, an Analog of Citric Acid.[1] Preparation of Optically Active Pyrrolidides of β-Phenylglutaric Acid

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RECEIVED DECEMBER 29, 1955

β-Phenylglutaric anhydride, taken as a model for citric acid and for other molecules of type Ca, b, d, d shows asymmetry in its reaction with *l*-menthol at 155°, leading to the diastereomeric mono-*l*-menthyl esters in unequal (54:46%) yields. Thus the enzymatic reactions of substrates of type Ca, b, d, d may take place at the two sites d at unequal rates not necessarily because of three point contact between the compound and the optically active enzyme, but possibly because of reaction *via* diastereomeric transition states. Separation of the diastereomeric mono-*l*-menthyl-β-phenylglutarates is a process similar to resolution, and reaction of the individual esters with lithium pyrrolidide leads to the optically active enantiomorphic mono-pyrrolidides of β-phenylglutaric acid.

Experiments with C^{14}-labeled citric acid prepared both biochemically[3] and from (−)γ-chloro-β-carboxy-β-hydroxybutyric acid,[4] (−)$ClCH_2C(OH)(COOH)CH_2COOH$, have confirmed that the enzymatic degradation of citric acid, $HO_2CCH_2C(OH)(CO_2H)CH_2CO_2H$, to α-ketoglutaric acid, $HO_2C\text{-}CO\text{-}CH_2CH_2CO_2H$, *via* aconitic and isocitric acids proceeds asymmetrically, the enzyme distinguishing between the two carboxymethyl groups. Similar specificity may be observed in other enzymatic processes—the conversion of serine, $CH_2(OH)CH(NH_2)CO_2H$ to glycine[5] possibly *via* the symmetric aminomalonic acid, and the stereospecific reduction[6] of the symmetric deuteroacetaldehyde, $CH_3CD{=}O$ by reduced diphosphopyridine nucleotide. This kind of stereochemical specificity is commonly attributed to a three point contact between substrate and enzyme.[7] These reactions, however, may be interpreted in terms of different rates of formation of diastereomeric transition states, although such analysis cannot disprove the three point contact mechanism.

Formation of diastereomers is very common and, requiring the formation of at least two centers of asymmetry in a transition state or product, may occur under conditions which include the following: (1) two reactants, each containing a center of asymmetry, combine, as in the common method of resolution of enantiomorphs *via* diastereomers.

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[1] While this work was in progress, the related study of the reaction of β-phenylglutaric anhydride with *l*-α-phenylethylamine was reported, P. Schwartz and H. E. Carter, *Proc. Nat. Acad. Sci.*, **40**, 499 (1954).

[2] Brandeis University, Waltham, Massachusetts.

[3] V. R. Potter and C. Heidelberger, *Nature*, **164**, 180 (1949).

[4] P. E. Wilcox, C. Heidelberger and V. R. Potter, THIS JOURNAL, **72**, 5019 (1950).

[5] D. Shemin, *J. Biol. Chem.*, **162**, 297 (1946).

[6] F. A. Loewus, F. H. Westheimer and B. Vennesland, THIS JOURNAL, **75**, 5018 (1953).

[7] A. G. Ogston, *Nature*, **162**, 963 (1948).