[Contribution from the Department of Chemistry of Cornell University]

Elimination Reactions of Bicyclic Quaternary Salts. V. The Synthesis and Base Degradation of 7,7-Dimethylpseudopelletierine Methiodide

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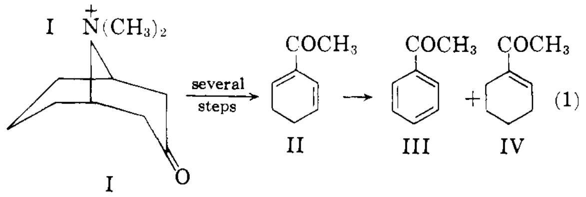
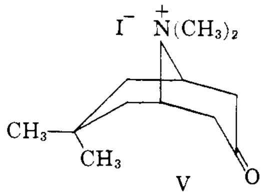
Two synthetic routes to 3,3-dimethylglutaraldehyde (IX) are reported. Under the Robinson–Schöpf "biogenetic" conditions, this dialdehyde is converted into 7,7-dimethylpseudopelletierine (X), characterized as its methiodide V. Base degradation of V yields an unstable liquid, $C_{10}H_{14}O$, shown to be 2-acetyl-5,5-dimethylcyclohexadiene-1,3 (XVI). A mechanism for this transformation, and its relation to the conversion of pseudopelletierine methiodide (I) into an equimolar mixture of acetophenone (III) and 1-acetylcyclohexene (IV) under analogous conditions, are discussed.

Introduction

In an earlier paper in this series,[2] it was shown that the base degradation of pseudopelletierine methiodide (I) gives rise to an equimolar mixture of acetophenone (III) and 1-acetylcyclohexene (IV). A rather involved reaction sequence, terminating in a base-catalyzed hydride ion exchange between two molecules of the hypothetical intermediate II, was suggested in explanation of this result[2] (see equation 1 for an outline of this mechanism; for a more detailed discussion see ref. 2.)



In an effort to learn more about this rather complex degradation, we have studied the synthesis and base degradation of 7,7-dimethylpseudopelletierine methiodide (V), a *gem*-dimethyl derivative of I in

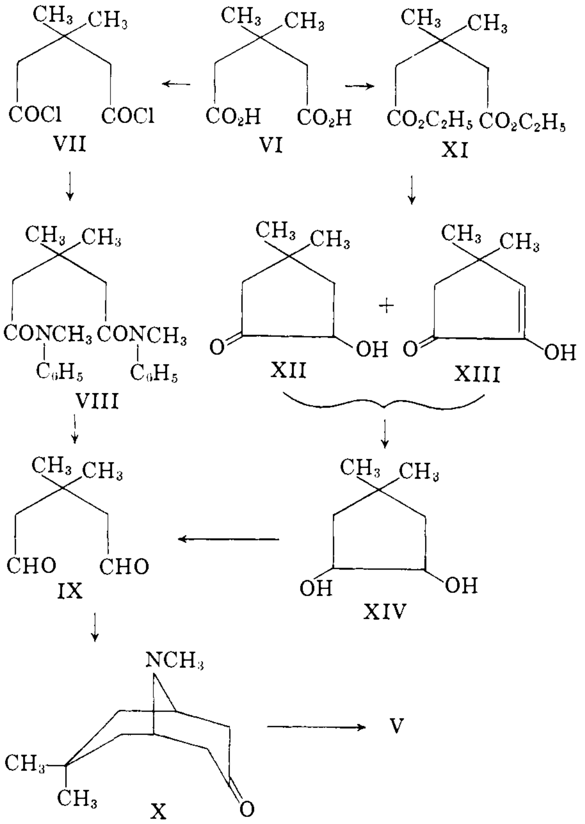


which a hydride transfer analogous to that postulated above is structurally forbidden.

Synthesis of 7,7-Dimethylpseudopelletierine Methiodide (V).—The synthesis of 7,7-dimethylpseudopelletierine followed the well-worn Robinson–Schöpf "biogenetic" pathway, using as the key intermediate 3,3-dimethylglutaraldehyde (IX). Two routes from 3,3-dimethylglutaric acid (VI) to the requisite dialdehyde, which turned out to be an extremely unstable liquid, were explored. The entire synthetic scheme is outlined in Chart I.

The first synthesis depended on the selective reduction of the bis-N-methylanilide of 3,3-dimethylglutaric acid (VIII → IX) with lithium aluminum hydride, following the technique of Weygand.[3] Although a variety of experimental conditions was used in an attempt to bring about the desired reduction in good yield, no really satisfactory procedure

Chart I



was developed. Even the best conditions found gave a mixture of starting material, dialdehyde and over-reduced product. Attempts to purify this product by distillation were unsuccessful except in one instance; the usual result was immediate polymerization of the distillate. In order to circumvent this difficulty, the crude lithium aluminum reduction product was treated directly with acetonedicarboxylic acid and methylamine in a buffered medium.[4] The 7,7-dimethylpseudopelletierine (X) produced in this way was converted directly into the desired methiodide V. Because of the difficulty in characterizing the intermediates in this sequence, as well as because of the rather low overall yield, an alternate synthetic route was sought.

Diethyl 3,3-dimethylglutarate (XI) was subjected to a homogeneous acyloin condensation, us-

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[1] Alfred P. Sloan Research Fellow.

[2] J. Meinwald and S. L. Emerman, This Journal, **78**, 5087 (1956).

[3] F. Weygand, G. Eberhardt, H. Linden, F. Schäfer and I. Eigen, *Angew. Chem.*, **65**, 525 (1953).

[4] The reaction conditions used for this condensation were those described by A. C. Cope, H. L. Dryden, Jr., and C. F. Howell, *Org. Syntheses*, **37**, 73 (1957), in their carefully worked out procedure for the synthesis of pseudopelletierine.

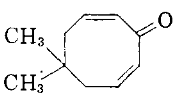
ing sodium in liquid ammonia–ether solution,[5] to give a mixture of 4,4-dimethylcyclopentan-2-ol-1-one (XII) and 4,4-dimethylcyclopentan-1,2-dione (XIII) in about 50% yield. This mixture was converted in 80% yield into 4,4-dimethylcyclopentan-1,2-diol (XIV) by successive reductions with Raney nickel and lithium aluminum hydride. Sodium bismuthate cleavage[6] of this diol afforded 3,3-dimethylglutaraldehyde (IX) satisfactorily. In view of the previously encountered instability of IX, the aqueous aldehyde solution resulting from the oxidative cleavage was used directly for the "biosynthesis." The tertiary base thus obtained was converted into the desired methiodide V in 30% over-all yield (from diol XIV) by treatment with methyl iodide in methanol.

The methiodide obtained *via* the acyloin route was significantly easier to purify than that prepared by the alternate technique; since the over-all yield by this method was also higher, it was adopted as the method of choice for the synthesis of V.

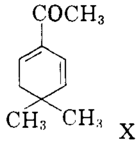
Base Degradation of 7,7-Dimethylpseudopelletierine Methiodide.—The base degradation of 7,7-dimethylpseudopelletierine methiodide was carried out using 10% barium hydroxide, following the procedure previously applied to pseudopelletierine methiodide (I) itself.[2] A neutral, liquid *product*, giving analytical figures corresponding to the molecular formula $C_{10}H_{14}O$, was obtained in good yield. In view of the difficulty previously encountered in recognizing the base degradation product of I to be a mixture,[7] special care was taken in this instance to establish the homogeneity of the product. A sharp-melting semicarbazone was obtained in good yield, and from it the original ketone was readily regenerated. The infrared spectrum of the regenerated material was essentially the same as that of the original degradation product. On distillation, both boiling points and refractive indices were steady. Finally, vapor chromatography at two temperatures on a Celite–silicone oil column gave only a single peak.

Evidence for the presence of two double bonds in the degradation product was provided by catalytic hydrogenation, which gave a saturated ketone shown to correspond to the formula $C_{10}H_{18}O$. The original dienone itself was somewhat unstable; on standing in air, the originally colorless, mobile, analytical sample was transformed into a greenish, viscous liquid, whose elementary analysis revealed over a 10% increase in oxygen content.

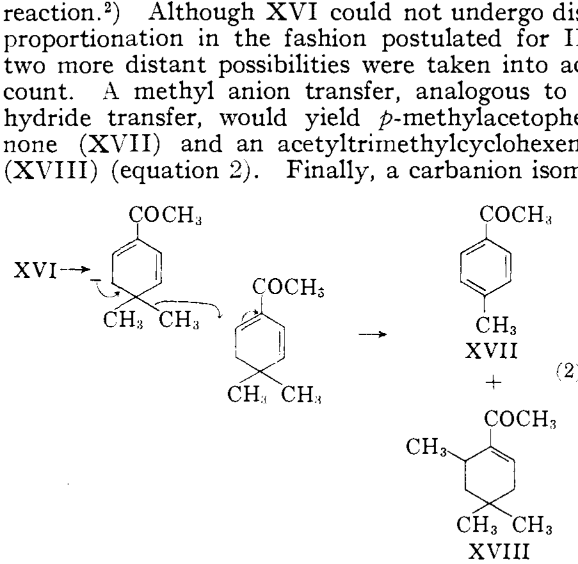
Several possible structures were considered for this labile dienone. If V had simply suffered a pair of normal β-eliminations, dimethylamine and 7,7-dimethylcycloöctadien-1,4-one-3 (XV) or possibly a double bond isomer[8] would be formed. Hydrolytic ring cleavage of XV, followed by a normal aldol cyclization to form a six-membered ring, would lead to 2-acetyl-5,5-dimethylcyclohexadiene-1,3 (XVI), analogous to the hypothetical cyclohexadiene intermediate II in the degradation of I. (Alternately, XVI might be formed *via* a transannular reaction.[2]) Although XVI could not undergo disproportionation in the fashion postulated for II, two more distant possibilities were taken into account. A methyl anion transfer, analogous to a hydride transfer, would yield *p*-methylacetophenone (XVII) and an acetyltrimethylcyclohexene (XVIII) (equation 2). Finally, a carbanion isomerization of the type shown in equation 3, related to the Stevens rearrangement, followed by oxidative aromatization, might lead from XVI to 3,4-dimethylacetophenone (XIX).

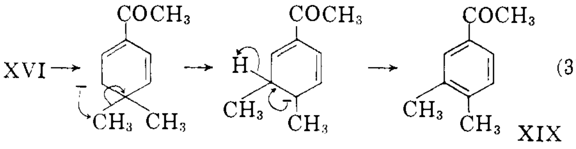


XV



XVI





The latter two possibilities (equations 2 and 3) were excluded easily. Thus, the homogeneity of the degradation product eliminated the disproportionation mixture (XVII + XVIII) from further consideration. Direct comparison of infrared spectra of the degradation product with those of authentic samples of *p*-methylacetophenone (XVII) and 3,4-dimethylacetophenone (XIX)[9] revealed striking differences. The only seriously contending structures were therefore the cycloöctadienones (XV, etc.) and the acetylcyclohexadiene XVI. Evidence in favor of XVI was provided by both chemical and physical studies, which will now be summarized.

The presence of a *conjugated* diene system was proved by treatment of the degradation product (hereafter designated as XVI) with two dienophiles. Thus, XVI reacted with N-phenylmaleimide and with tetracyanoethylene[10] to give crystalline 1:1 adducts to which structures XX and XXI may be assigned. The presence of an α,β-unsaturated ketone chromophore in XXI is indicated by

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[5] J. C. Sheehan and R. C. Coderre, This Journal, **75**, 3997 (1953).

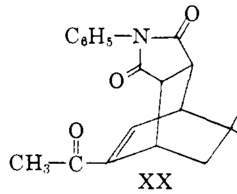
[6] W. Rigby, *J. Chem. Soc.*, 1907 (1950).

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

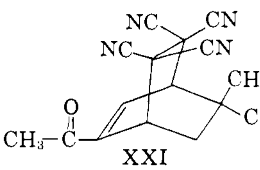
[8] Structures with either or both of the double bonds of XV moved into β,γ-positions should also be included (*cf.* J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, This Journal, **77**, 4401 (1955)).

[9] The authors are grateful to Professor W. G. Brown for providing an authentic sample of this ketone.

[10] The authors are grateful to Dr. Yvonne C. Meinwald for a gift of tetracyanoethylene.



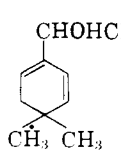
XX



XXI

its ultraviolet absorption spectrum ($\lambda_{\max}^{\text{EtOH}}$ 221 mμ, log ε 4.10).[11]

Further chemical evidence supporting structure XVI was obtained by sodium borohydride reduction of the degradation product. This yielded the corresponding alcohol XXII, whose ultraviolet absorption spectrum ($\lambda_{\max}$ 257 mμ, log ε 3.29) confirmed the presence of a cyclohexadiene system.[12] "Active" manganese dioxide reoxidized XXII to a carbonyl compound, as expected for an allylic alcohol.[13] Finally, catalytic hydrogenation of XXII resulted in the uptake of two moles of hydrogen, and produced a saturated alcohol which gave a positive iodoform test, as expected for the $-CHOHCH_3$ grouping.



XXII

The nuclear magnetic resonance spectrum of XVI provided an independent confirmation of its constitution.[14] The spectrum consisted of four groups of peaks (see Fig. 1). At highest field strength the single, intense peak may be attributed to the six equivalent protons of the *gem*-dimethyl group. The following pair of peaks appear to correspond to the five protons of the remaining methyl group (adjacent to the carbonyl function) and the lone methylene group. Proceeding to lower fields, a quartet of lines appears which may be associated with the two non-equivalent olefinic protons on C_3 and C_4. Since these protons have somewhat different environments, they would be expected to show spin–spin splitting. The appearance of a quartet, with weak outer lines and intense inner lines, corresponds to expectations for such a pair of protons with the spin–spin coupling constant and the chemical shift of similar values.[15] Finally, the triplet showing a 1:2:1 intensity ratio, at lowest field, corresponds to expectation for the unique olefinic proton at C_1, split by coupling with the two adjacent protons of the C_6-methylene group.

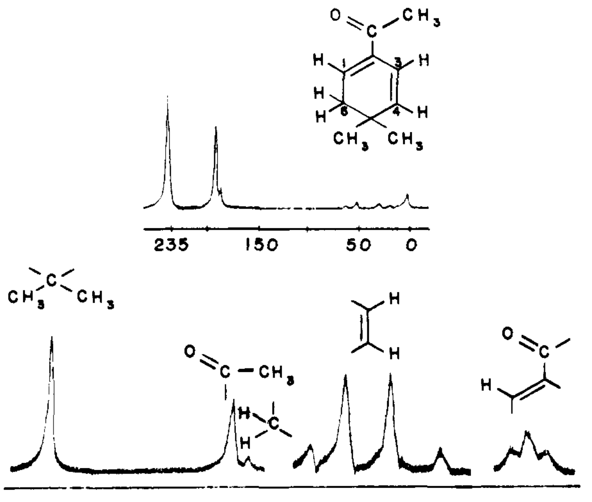


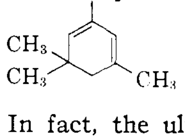
Fig. 1.—Proton magnetic resonance spectrum of 2-acetyl-5,5-dimethylcyclohexadiene-1,3 (XVI) at 40 Mc. (9,400 gauss): upper curve, total spectrum with peak at 0 = benzene (reference), scale in c.p.s.; lower curve, composite spectrum showing individual groups of peaks in greater detail.

Conclusions

On the basis of all of the above evidence, the identification of the 7,7-dimethylpseudopelletierine methiodide degradation product as 2-acetyl-5,5-dimethylcyclohexadiene-1,3 (XVI) seems secure. This finding helps confirm mechanism 1 for the base degradation of pseudopelletierine methiodide itself, and in particular provides strong support for the role of 2-acetylcyclohexadiene-1,3 (II) as an intermediate in that transformation.

Appendix.—In connection with this research, the ultraviolet spectrum of the cross-conjugated dienone XVI has been examined. This spectrum is of interest, since no simple compounds with this type of chromophore seem to have been studied. There is, in fact, very little on which to base a prediction for the spectrum of XVI, and for this reason its ultraviolet absorption was not discussed above in connection with the structure proof.

The two individual chromophores, if isolated from each other might be expected to give rise to absorption at ~256 mμ (cyclohexadiene)[12] or ~232 mμ (acetylcyclohexene).[11] On the other hand, if it is presumed that a ketone will show maximal absorption at ~15–20 mμ longer wave lengths than a corresponding acid, then a prediction for XVI based on the report for the cross-conjugated acid XXIII ($\lambda_{\max}$ 264 mμ)[16] would be in the region of 280 mμ. In fact, the ultraviolet spectrum of XVI revealed $\lambda_{\max}^{\text{EtOH}}$ 286 mμ, log ε 3.38 and $\lambda_{\min}^{\text{EtOH}}$ 255 mμ, log ε 3.06. These figures may be of some



XXIII

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(11) Acetylcyclohexene shows $\lambda_{\max}^{\text{EtOH}}$ 232 mμ, log ε 4.10 (E. A. Braude, E. R. H. Jones, F. Sondheimer and J. B. Toogood, *J. Chem. Soc.*, 607 (1949)). The difference of 11 mμ between the absorption maximum of XXI and the simpler model compound can probably be attributed to the presence of the nearby but unconjugated nitrile groups, although no detailed rationalization of the hypsochromic shift can be offered.

(12) *Cf.* 1,3-cyclohexadiene: $\lambda_{\max}^{\text{hexane}}$ 256 mμ, log ε 3.9 (V. Henri and L. W. Pickett, *J. Chem. Phys.*, **7**, 439 (1939)); α-phellandrene: $\lambda_{\max}^{\text{EtOH}}$ 263 mμ, log ε 3.4 (H. Booker, L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940)). The somewhat low intensity of the absorption of alcohol XXII may be due to the presence of some over-reduced material or other non-absorbing contaminant.

(13) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *ibid.*, 1094 (1952).

(14) The authors are indebted to Mr. L. D. Fergesen for his enthusiastic coöperation in carrying out the n.m.r. study.

(15) For a convenient, brief discussion of this point see J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 55–56.

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

utility in recognizing the presence of this rather special chromophore in more complex systems.

Experimental

3,3-Dimethylglutaryl Chloride (VII).—3,3-Dimethylglutaric acid[17] was converted into the corresponding acid chloride using phosphorus pentachloride as described by Tschudi and Schinz.[18] 3,3-Dimethylglutaryl chloride, b.p. 59–60° (0.8 mm.), n^{25}D 1.4661 (lit.[17,19] b.p. 95–96° (11 mm.), 74–76° (2 mm.)), was obtained in 89% yield.

3,3-Dimethylglutaric Acid Bis-N-methylanilide (VIII).—N-Methylaniline (59.3 g., 0.55 mole) and an excess of pyridine (200 ml.) were dissolved in 700 ml. of dry benzene. 3,3-Dimethylglutaryl chloride (52 g., 0.26 mole) was added slowly, and the resultant mixture was heated to 60–70° for 45 min. The reaction mixture was poured into 1 l. of water, the organic layer separated, and the aqueous layer extracted with 200 ml. of benzene. The combined benzene layers were washed three times with 200 ml. of 2 *N* hydrochloric acid, twice with 200 ml. of 10% sodium bicarbonate and twice with 200 ml. of water. After the benzene solution was dried over anhydrous magnesium sulfate, the solution was concentrated to a small volume (*ca.* 100 ml.) and 250 ml. of hexane was added. This addition resulted in the immediate precipitation of 76 g. (84%) of the diamide VIII, m.p. 101–103°. After recrystallization from ethyl acetate and hexane, the melting point was raised to 104.5–105°.

Anal. Calcd. for $C_{21}H_{26}O_2N_2$: C, 74.54; H, 7.72; N, 8.28. Found: C, 74.51; H, 7.97; N, 8.35.

3,3-Dimethylglutaraldehyde (IX) by Lithium Aluminum Hydride Reduction of VIII.[3]—A solution of 23.7 g. (0.070 mole) of VIII in 200 ml. of dry tetrahydrofuran was cooled to 0°, and a solution of 1.76 g. (0.046 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran was added slowly with cooling. After the addition was complete, the mixture was stirred at room temperature for 22 hours. The reaction mixture was hydrolyzed with 20 ml. of saturated sodium sulfate solution, and 100 ml. of 2 *N* sulfuric acid was added. The resultant solution was then extracted with several portions of ether. After the ether extract was dried over anhydrous magnesium sulfate, the solvent was distilled off, leaving 8.0 g. of crude product. This material showed 5.95 μ (amide) absorption in the infrared as well as the desired 5.70 μ (aldehyde) absorption. A bis-2,4-dinitrophenylhydrazone, which showed m.p. 238–239° after recrystallization from dioxane, was readily prepared.

Anal. Calcd. for $C_{19}H_{20}O_8N_8$: C, 46.60; H, 4.10; N, 22.90. Found: C, 46.70; H, 4.28; N, 23.02.

On distillation of the crude dialdehyde, 2.5 g. (28%) of viscous product, b.p. 35–40° (0.6 mm.), was obtained. This material showed the characteristic aldehyde peak at 5.70 μ, but was free of 5.95 μ absorption. Other attempts to distil the raw dialdehyde were unsuccessful due to polymerization during the distillation.

Diethyl 3,3-Dimethylglutarate (XI).—3,3-Dimethylglutaric acid (160 g., 0.625 mole), 125 ml. of absolute ethanol (1.88 moles), 500 ml. of benzene and 30 ml. of concentrated sulfuric acid were mixed and refluxed for two days in a flask provided with an azeotropic water separator. Water was drawn off from time to time. After the excess benzene and ethanol were removed under reduced pressure, the residue was distilled, giving 118 g. (88%) of diethyl 3,3-dimethylglutarate, b.p. 83.5–85° (0.45 mm.), n^{25}D 1.4252 (lit.[20] b.p. 170–172° (100 mm.)).

Acyloin Reduction of Diethyl 3,3-Dimethylglutarate.[5]—To a dry, 5-l. three-necked flask fitted with a Dry Ice condenser, stirrer, addition funnel and nitrogen inlet, was added 1 l. of anhydrous ether and 1.5 l. of anhydrous ammonia. Freshly cut sodium (10.7 g., 0.464 mole) was added in small pieces with stirring. The system was swept thoroughly with pre-purified nitrogen for 30 minutes, and all subsequent operations up to the final extraction were carried out under a slow stream of nitrogen. A solution of diethyl 3,3-dimethylglutarate (20 g., 0.093 mole) in 500 ml. of ether was added with continuous stirring, over a period of 3 hours. The reaction mixture was then stirred overnight, allowing the ammonia to evaporate. When most of the ammonia had evaporated, a faintly yellow liquid remained. A solution of 10 ml. of methanol in 200 ml. of ether was added to destroy the excess sodium. This was followed by acidification with 100 ml. of 6 *N* hydrochloric acid. The salt which separated at this point was redissolved by the addition of 50 ml. of water. After separation of the aqueous and ether layers, the methanol and ethanol were distilled from the aqueous layer, which was then saturated with ammonium chloride and extracted twice with 100 ml. of ether and four times with 50 ml. of ether. The combined ether extract, dried over anhydrous magnesium sulfate, was evaporated to give 10.2 g. (87%) of crude product. On distillation of this material, 6 g. (52%) of a slightly yellow liquid, b.p. 76–80° (8 mm.), n^{25}D 1.4632–1.4595, was obtained. The distillate gave a deep purple ferric chloride test. It showed infrared absorption bands at 2.91, 5.75, 5.83, 6.02 and 6.12 μ.

In subsequent experiments, 50- to 60-g. portions of diester were used in the same volume of solvent. The yields in these runs ranged from 35–39%.

4,4-Dimethylcyclopentan-1,2-diol (XIV).—Three heaping teaspoonfuls of Raney nickel was suspended in 250 ml. of 95% ethyl alcohol containing 10 g. of acyloin product. The mixture was shaken with hydrogen in a Parr apparatus, and a 6 lb. pressure drop (6.4 lb. corresponded to one molar equivalent) was recorded within three hours. No significant further uptake occurred overnight, and the catalyst was filtered off and washed with ethanol. Evaporation of the solvent gave 9.5 g. (92%) of crude reduced product with strong hydroxylic absorption at 2.9 μ and weak carbonyl absorption at 5.75 μ. This material, which gave a negative ferric chloride test, was further reduced by treatment with lithium aluminum hydride as described below.

To 11 g. (0.282 mole) of lithium aluminum hydride in 200 ml. of dry ether was added 18.8 g. (0.141 mole) of Raney nickel reduced acyloin product (obtained in two runs) in 200 ml. of ether. The addition, carried out so as to maintain constant refluxing, required 1.5 hours. After the mixture was stirred overnight, 44 ml. of water was added dropwise with external ice cooling. After an additional hour of stirring, inorganic salts were removed by filtration and washed well with ether. The ethereal filtrate was dried over anhydrous magnesium sulfate. After removal of the solvent, 17.2 g. (95%) of crude product, free of carbonyl absorption in the infrared, remained behind. On distillation, 12.9 g. (69%) of 4,4-dimethylcyclopentan-1,2-diol (XIV), b.p. 106–108° (5 mm.), was obtained. The distillate froze to a white, camphor-like, crystalline solid, which melted slightly above room temperature.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.28; H, 10.67.

Sodium Bismuthate Oxidation of 4,4-Dimethylcyclopentan-1,2-diol.[6]—4,4-Dimethylcyclopentan-1,2-diol (XIV) (18 g., 0.139 mole) was suspended in 60 ml. of water and 60 ml. of $3^1/_3$ *M* phosphoric acid. Sodium bismuthate (19.9 g., 0.0695 mole) was added in small portions with stirring. When the reaction mixture turned from a light brown to a pale beige color, another 60 ml. of $3^1/_3$ *M* phosphoric acid was added, followed by the slow addition of a second 19.9-g. portion of sodium bismuthate. After 1.5 hours, the light beige reaction mixture was filtered through a sintered glass funnel. The inorganic residue was washed five times with 20-ml. portions of 50% ethyl alcohol. The dialdehyde solution thus obtained was used directly for the subsequent "biosynthesis."

In order to confirm that the desired dialdehyde had been produced, 2 ml. of the above solution was added to a fresh solution of 2,4-dinitrophenylhydrazone reagent. The resultant orange precipitate, after recrystallization from dioxane, was identical in all respects with an authentic sample of 3,3-dimethylglutaraldehyde 2,4-dinitrophenylhydrazone.

7,7-Dimethylpseudopelletierine (X) and 7,7-Dimethylpseudopelletierine Methiodide (V).[4]—The 3,3-dimethylglutaraldehyde solution obtained from sodium bismuthate oxidation of 18 g. of 4,4-dimethylcyclopentan-1,2-diol (XIV) was placed in a 2-l. three-necked flask fitted with stirrer, and neutralized with 6 *N* sodium hydroxide. To the solution was added 20 g. (0.139 mole) of acetonedicarboxylic acid in 200 ml. of water, 10 g. (0.139 mole) of methylamine hydrochloride in 100 ml. of water and 7 g. of disodium hydrogen phosphate plus 4 g. of monopotassium dihydrogen phosphate in 110 ml. of water. The *p*H of the solution rose from

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[17] W. T. Smith and G. L. McLeod, *Org. Syntheses*, **31**, 40 (1951).

[18] G. Tschudi and H. Schinz, *Helv. Chim. Acta*, **33**, 1865 (1950).

[19] H. Stetter and H. J. Krause, *Chem. Ber.*, **87**, 209 (1954).

[20] W. H. Perkin, Jr., *J. Chem. Soc.*, **69**, 1475 (1896).

2 to a constant value of 5.5 in about a 3-hour period. After the mixture had stirred under nitrogen for two days, the aqueous solution was brought to *p*H 2, and the ethanol was removed under reduced pressure. On cooling, the solution was made basic (*p*H 12) by addition of 50% sodium hydroxide and extracted thoroughly with methylene chloride. Evaporation of the methylene chloride, after drying over anhydrous magnesium sulfate, gave 18.8 g. of crude 7,7-dimethylpseudopelletierine as a viscous red liquid. To this crude product was added 50 ml. of methyl iodide and 20 ml. of methanol. A yellow crystalline precipitate of methiodide appeared within 10 minutes. After standing overnight, the precipitate was filtered, giving 13.8 g. (31% based on diol used) of 7,7-dimethylpseudopelletierine methiodide (V), m.p. 215–220°. After three recrystallizations from methanol, a constant melting (230–231°) analytical sample was obtained.

Anal. Calcd. for $C_{12}H_{22}ONI$: C, 44.59; H, 6.87; N, 4.33; I, 39.26. Found: C, 44.62; H, 6.64; N, 4.16; I, 39.05.

In another experiment, the crude tertiary amine isolated from the "biosynthesis" was distilled, giving a main fraction of X showing b.p. 102° (0.45 mm.) and an infrared maximum at 5.87 μ.

When the biosynthetic reaction was carried out using the crude dialdehyde directly as obtained from lithium aluminum hydride reduction of 3,3-dimethylglutaric acid bis-N-methylanilide (VIII), a 5% yield of methiodide V (based on VIII) was obtained. This product was, however, rather difficult to purify.

2-Acetyl-5,5-dimethylcyclohexadiene-1,3 (XVI).[2]—Barium hydroxide (25 g.) was dissolved in 250 ml. of boiling water. Recrystallized 7,7-dimethylpseudopelletierine methiodide (V, 5 g.) was added, and the mixture was subjected to steam distillation for 45 minutes. The combined distillate from two consecutive runs was extracted with five 150-ml. portions of ether. The ethereal solution was washed with 2 *N* hydrochloric acid and 10% sodium bicarbonate, and then dried over anhydrous magnesium sulfate. After evaporation of the ether, 4.0 g. (86%) of a pale yellow liquid was obtained. This material showed characteristic infrared maxima at 3.25, 3.35, 3.46, 3.54, 5.95 and 6.25 μ.

On distilling, a total of 3.4 g. of product was collected as six arbitrarily cut fractions, b.p. 79.5–81° (5 mm.), $n^{24}D$ 1.4872–1.4880. The infrared spectra of the distilled fractions were the same as that of the total crude product; ultraviolet absorption: λ_{max}^{EtOH} 286 mμ, log ϵ 3.38; λ_{min}^{EtOH} 255 mμ, log ϵ 3.06.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.25; H, 9.34.

The analytical sample, standing in air for several weeks, formed a yellow, sticky material. Reanalysis of this product indicated a considerable uptake of oxygen.

Anal. Found: C, 68.9, 68.5; H, 8.11, 8.30.

A 2,4-dinitrophenylhydrazone of XVI was prepared by the standard procedure. A bright red derivative, m.p. 172–176°, was obtained. Chromatography on Florisil gave only one component; ultraviolet absorption: λ_{max}^{EtOH} 373–380 mμ, log ϵ 4.31; λ_{max}^{EtOH} 310 mμ, log ϵ 3.47.

The semicarbazone of XVI, m.p. 186–192°, was prepared in the usual manner. Recrystallization from ethanol gave an analytical sample, m.p. 198–200°; ultraviolet absorption: λ_{max}^{EtOH} 242 mμ, log ϵ 4.28; λ_{max}^{EtOH} 277–278 mμ, log ϵ 4.19.

Anal. Calcd. for $C_{11}H_{17}ON_3$: C, 63.68; H, 8.27; N, 20.27. Found: C, 63.88; H, 8.33; N, 20.43.

Steam distillation of 1.94 g. of this semicarbazone from a solution of 7.6 g. of phthalic anhydride in 250 ml. of water afforded 1.14 g. (81%) of XVI as a colorless liquid after the usual workup. This regenerated ketone was vacuum distilled and divided into four arbitary fractions (total recovery 0.90 g.). These fractions showed a slightly higher refractive index range ($n^{25}D$ 1.4915–1.4920) than the original product, but had the same ultraviolet absorption spectrum. The infrared spectra were essentially the same as that of the original, crude product, except for the disappearance of both a shoulder at 6.05 μ and a small peak at 11.8 μ. For comparison purposes, the infrared spectra of *p*-methylacetophenone (XVII) and 3,4-dimethylacetophenone (XIX)[9] were taken and compared with that of XVI. The strong absorption band at 12.20 μ characteristic of the two aromatic compounds was absent in the spectrum of XVI.

Vapor chromatography of the different distilled fractions at 208°, on a Celite–silicone oil column, gave a single peak with a retention time of 12 minutes. At 190°, a single peak with an 18.3-minute retention time was observed.

The nuclear magnetic resonance spectrum of XVI was obtained using a Varian high-resolution n.m.r. spectrometer (40 Mc.) (see Fig. 1).

Diels–Alder Adduct (XX) of 2-Acetyl-5,5-dimethylcyclohexadiene-1,3 (XVI) and N-Phenylmaleimide.—N-Phenylmaleimide (0.38 g.) and 0.32 g. of XVI were dissolved in 12 ml. of benzene and refluxed under nitrogen in a flask protected by a calcium chloride drying tube for 7 days. At the end of this period, a small amount of precipitate seemed to have separated out. Most of the benzene was removed under reduced pressure, and the resulting precipitate was recrystallized from benzene, giving 0.25 g. (36%) of product, m.p. 177–178°. A constant melting analytical sample of the adduct, m.p. 183–185°, was obtained by three crystallizations from benzene.

Anal. Calcd. for $C_{20}H_{21}O_3N$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.32; H, 6.37; N, 4.41.

Diels–Alder Adduct (XXI) of 2-Acetyl-5,5-dimethylcyclohexadiene-1,3 (XVI) and Tetracyanoethylene.—A mixture of 0.30 g. of XVI and 0.34 g. (0.25 g. required) of tetracyanoethylene,[10] dissolved in 20 ml. of benzene, was refluxed for 7 days. Crystals of adduct slowly appeared on the wall of the flask during this period. After the usual isolation procedure, the crude product was recrystallized from 95% ethyl alcohol and decolorized with charcoal to give 0.17 g. (31%) of white crystalline adduct, m.p. 191.5–192°. A mixture melting point with pure tetracyanoethylene (m.p. 197.5–198°) showed a strong depression (149–150°); ultraviolet absorption: λ_{max}^{EtOH} 221 mμ, log ϵ 4.1.

Anal. Calcd. for $C_{16}H_{14}ON_4$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.85; H, 5.10; N, 20.29.

Semi-micro Hydrogenation of 2-Acetyl-5,5-dimethylcyclohexadiene-1,3.—A suspension of 0.111 g. of Adams catalyst in 10 ml. of ethyl acetate was pre-reduced in a standard, semi-micro hydrogenator. A solution of 0.147 g. of distilled XVI in 5 ml. of ethyl acetate was added. A total of 55 ml. (2.5 molar equivalents) of hydrogen was absorbed in 2.5 hours. The recovered reduced product (0.120 g.) was characterized as its 2,4-dinitrophenylhydrazone, of which an analytical sample, m.p. 111.5–112.5°, was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{22}O_4N_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.35; H, 6.77; N, 16.52.

Sodium Borohydride Reduction of 2-Acetyl-5,5-dimethylcyclohexadiene-1,3.—Sodium borohydride (1.77 g., 0.046 mole), dissolved in 6 ml. of ethanol and 8 ml. of water, was added slowly to a solution of 3.5 g. (0.023 mole) of XVI in 6 ml. of ethanol at 0°. After the addition was completed, the solution was stirred at room temperature for four hours, and then neutralized with 10% sulfuric acid. The mixture was then saturated with ammonium sulfate and extracted four times with 50-ml. portions of methylene chloride. After the methylene chloride solution had been dried over anhydrous magnesium sulfate, the solvent was removed, leaving 3.4 g. (91%) of crude product. The infrared spectrum of this material showed strong hydroxylic absorption at 2.90 μ, and no carbonyl peak. Distillation gave 1.73 g. (51%) of XXII, b.p. 77.5° (3 mm.), $n^{25}D$ 1.4767–1.4770; ultraviolet absorption: λ_{max}^{EtOH} 256 mμ, log ϵ 3.29; λ_{min}^{EtOH} 224 mμ, log ϵ 2.82.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 77.86; H, 11.04.

A 3,5-dinitrobenzoate was prepared in the usual manner. This derivative was very difficult to crystallize, but finally yielded crystals, m.p. 77–79°, from heptane. An analytical sample, m.p. 87–88°, was obtained from ethanol.

Anal. Calcd. for $C_{17}H_{18}O_6N_2$: C, 58.95; H, 5.24; N, 8.09. Found: C, 58.67; H, 5.24; N, 8.25.

A small sample of XXII reacted slowly with N-phenylmaleimide in benzene to give an adduct, m.p. 164–165°, in about 20% yield. The quantity obtained was too small for complete purification of an analytical sample.

Anal. Calcd. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12. Found: C, 74.85; H, 7.43.

Catalytic reduction of 0.45 g. of XXII in ethyl acetate over pre-reduced Adams catalyst resulted in the uptake of 126 ml. (2 molar equivalents) of hydrogen. The recovered product (0.35 g.) reacted with sodium hypoiodite in aqueous dioxane to give a yellow solid, m.p. 121–122°, identified as iodoform (lit.[21] m.p. 119–121°).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Ion-Pair Formation in the Reactions of Alkyl Iodides with Silver Salts

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The reactions of silver nitrate and silver perchlorate with methyl, ethyl, isopropyl and neopentyl iodides have been studied. The effects of added salts, the fact that silver nitrate reacts more rapidly than silver perchlorate, and the low reactivity of neopentyl iodide, all indicate that the reactions have some SN2-character. Third-order kinetics cannot be documented clearly because variations in ionic strength are not controllable. However, the kinetic data are best rationalized by a mechanism in which both silver cations and the accompanying anions participate in the rate-determining step of the reactions. The results, combined with data from the literature, are interpreted in terms of a mechanism in which the first-formed product is an ion pair composed of an anion and a carbonium ion.

Kinetic studies of the reactions of silver nitrate,[2–12] silver perchlorate[13] and other silver salts[14] with alkyl halides, although numerous, have left a rather clouded picture as to the actual mechanism(s) of such reactions. The view that they are "SN1-like" is widely held[15] and is largely due to the familiar sequence of reactivities, tertiary > secondary > primary, which is observed when alkyl halides are treated with an alcoholic solution of silver nitrate.[16] This qualified statement has often been extended to the specification of a mechanism including the intermediate production of a carbonium ion.

$$R\text{-}X + Ag^+ \longrightarrow R^+ + AgX \qquad (1)$$

$$R^+ + Y^- \longrightarrow R\text{-}Y \qquad (2)$$

Kornblum, *et al.*,[14] have argued that SN1-like reactivity cannot be considered as diagnostic for a mechanism involving free carbonium ions. They maintain that the transition states for concerted reactions may, in some instances, involve the development of large amounts of carbonium ion character in the substrate undergoing substitution. This is quite consistent with most modern views of the continuity in mechanism in all nucleophilic displacement reactions.[17] Particular stress is laid on the low reactivity of neopentyl iodide toward silver nitrite since the phenomenon is indicative of a steric barrier to the reaction similar to that observed in displacements, such as halide exchanges in non-hydroxylic solvents, which are classic examples of limiting SN2 reactions.

The study of these reactions by conventional kinetic methods has been regarded as rather difficult and even under the most favorable circumstances is somewhat unsatisfying. Heterogeneity is the greatest problem, although it does not seem to be as universally troublesome as has often been supposed. Most silver salts are but sparingly soluble, especially in organic solvents, so many observations have been made with a reactant in the solid phase. Kornblum, *et al.*, strongly suggest that under such circumstances the reactions are likely to occur on the surface of the solid reactant. If such is the case, kinetic analysis will be complex and is likely to yield little information concerning the molecularity with respect to the reagent except for those conclusions which may be inferred from relative reactivities. The very high solubility of silver salts in acetonitrile and the generally great solubility of silver nitrate and silver perchlorate do provide a means of carrying out kinetic studies in solutions which are, at the outset, homogeneous. Since solid silver halide will always be deposited throughout the reaction, two new problems arise. First, the solid silver halide may provide a surface on which reaction may occur and, second, it is virtually impossible to maintain constant ionic strength throughout the reaction. Catalysis by precipitated silver halide has often been reported.[4,18,19]

Consideration of the details of various investigations leaves many questions as to the actual status of this problem. Donnan and Burke[2] studied the reactions of silver nitrate with various alkyl iodides in alcohol and alcohol–water solutions. Their

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