# Nuclear Magnetic Resonance Studies of Some Condensation Products of 2,4-Pentanedione with Formalin and Acetaldehyde

J. K. O'LOANE, C. M. COMBS, AND R. L. GRIFFITH

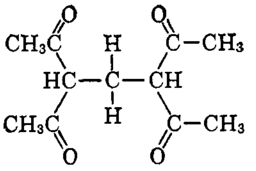
*Contribution No. 2277 from the Kodak Research Laboratories, Eastman Kodak Company, Rochester, New York 14650*

*Received November 23, 1962*

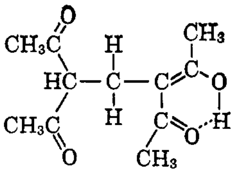
High-resolution proton magnetic resonance (n.m.r.) spectra have been obtained and interpreted for two tautomers of 3,5-diacetyl-2,6-heptanedione, 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone, and 3-acetyl-3-penten-2-one. The tautomeric forms of the two diacetylheptanediones have been established. Long-range spin-spin coupling through four σ-bonds was observed for the hydroxyl group of 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone. Two different carbonyl absorptions in the infrared spectrum and two different acetyl absorptions in the n.m.r. spectrum were found for 3-acetyl-3-penten-2-one. Changes in the hydroxyl and acetyl resonance positions with solvent and on dilution were studied for various alcohols and ketones.

In an investigation of the reaction between formalin and 2,4-pentanedione, Wilson[1] obtained four crystalline products melting at 41.5–42.5°, 55–56°, 89–90°, and 176–177°.

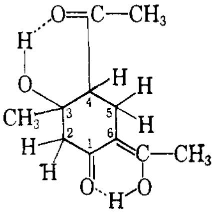
The analyses fit the formula $C_{11}H_{16}O_4$ for the first three products and $C_{17}H_{24}O_6$ for the last. On the basis of the n.m.r. spectra the structures proposed for the first three are, respectively, I, II, and III following. No structure is proposed for the fourth.



I, m.p. 41.5–42.5°



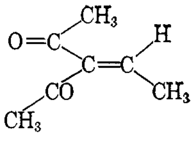
II, m.p. 55–56°



III, m.p. 89–90°

The first two products were obtained in the absence of any catalyst. The third and fourth were isolated when the condensation was catalyzed by different basic materials. Because of their high stability, these tautomers can be isolated as pure individuals and their n.m.r. spectra can be determined with little, if any, interconversion.

A fifth compound, b.p. 44–45° (0.04 mm.), was obtained in a reaction between 2,4-pentanedione and acetaldehyde. The structure deduced from its n.m.r. spectrum is shown.



## Experimental

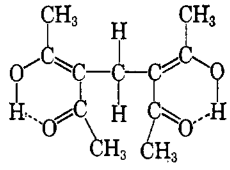
All spectra were obtained at 60 Mc./sec. with a Varian dual purpose V-4302 n.m.r. spectrometer. The spectra of 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone, as well as those of the ketones and alcohols used as model compounds to determine the hydroxyl resonance positions, were obtained with the spectrometer equipped with a field homogeneity control unit.

Calibration of spectra was done by the side-band modulation technique,[2] with 3% by volume of tetramethylsilane (TMS) as an internal reference in all samples. The Hewlett-Packard wide range oscillator, Model 200 CD, was checked at all times against a Hewlett-Packard electronic counter, Model 521C. The average (within replicate) standard deviation of our measurements, based on three solutions of the substituted methylcyclohexanone, is 0.4 c.p.s. at 60 Mc. (0.0067 p.p.m.). Spectra were run at 22°.

**Materials.**—In addition to the compounds mentioned previously, 3-methyl-2,4-pentanedione and 1-methylcyclohexanol were prepared in these laboratories by B. D. Wilson and S. W. Cowan, respectively. 2-Pentanol was obtained from Columbia Organic Chemicals and 4-hydroxy-2-pentanone from K. and K. Laboratories. The other compounds used were Eastman Grade chemicals, except for carbon tetrachloride, methylene chloride, and acetonitrile, which were Spectro Grade, and 2-pentanone, which was Eastman practical grade. They were used without further purification.

## Discussion

**Spectra of the Heptanediones.**—The two compounds obtained without a basic catalyst might be two of the three following tautomers: I, a tetraketo; II, a monoenol H-bonded internally; or IV, a dienol H-bonded internally.



IV

**A. Compound Melting at 55–56° (II).**—Data from the n.m.r. spectrum of this compound in 30% solution in methylene chloride are given in Table I. The data in Table II show that the resonance position for an enolic hydroxyl of a β-diketone occurs at approximately −15 to −17 p.p.m. relative to TMS. Therefore, the peak at −17 p.p.m. indicates strongly that the compound melting at 55–56° exists as an enolized β-diketone in methylene chloride solution.[3]

The following observations show that this compound is the monoenol II rather than the dienol IV: (1) the presence of two singlets of about equal intensity at

---

[1] B. D. Wilson, *J. Org. Chem.*, **28**, 314 (1963).

[2] J. T. Arnold and M. G. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).

[3] (a) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Am. Chem. Soc.*, **71**, 1068 (1949); (b) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 142.

TABLE I

CHEMICAL SHIFTS[a] OF TWO TAUTOMERS OF 3,5-DIACETYL-2,6-HEPTANEDIONE[b]

| P.p.m. | Band contour | Assignment |
|---|---|---|
| | Compound II, m.p. 55–56° | |
| −2.155 | Singlet | Enol $CH_3$− |
| −2.193 | Singlet | Keto $CH_3$− |
| −2.747 | Doublet | —$CH_2$— |
| −2.867 | | |
| −3.818 | Triplet | $-\underset{|}{\overset{|}{\mathrm{C}}}\mathrm{H}$ |
| −3.925 | | |
| −4.052 | | |
| −16.908 | Singlet | Chelated OH |
| | Compound I, m.p. 41.5–42.5° | |
| −2.188 | Singlet | Keto $CH_3$− |
| (−2.13)[c] | Triplet | —$CH_2$— |
| (−2.23)[c] | | |
| −2.348 | | |
| −3.565 | Triplet | $-\underset{|}{\overset{|}{\mathrm{C}}}\mathrm{H}-$ |
| −3.660 | | |
| −3.768 | | |

[a] Relative to TMS as internal standard. [b] 30% in $CH_2Cl_2$, 3% TMS. [c] Hypothesized.

TABLE II

HYDROXYL RESONANCE POSITIONS[a] IN ALCOHOLS AND KETONES

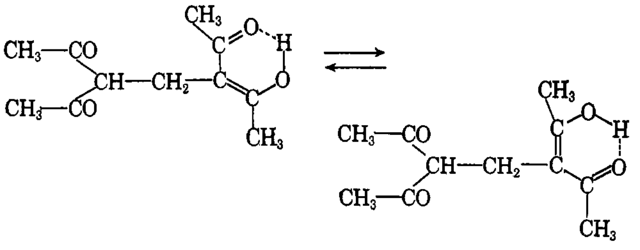
| | | Solvent | | | |
|---|---|---|---|---|---|
| | | $CCl_4$, mole % | | $CH_2Cl_2$, mole % | |
| | Neat | 12.5 | 2.5 | 8.5 | 1.7 |
| Acetylacetone | −15.463 | | | | |
| 3,5-Diacetyl-2,6-heptanedione (m.p. 55–56°) | | | | −16.908 | |
| 3-Methyl-2,4-pentanedione | −16.505 | | | −15.217 | −15.220 |
| 2-Acetylcyclohexanone | | | −15.683 | −15.902 | −15.922 |
| *o*-Hydroxyacetophenone | −12.170 | | −12.067 | −12.220 | −12.232 |
| 4-Hydroxy-4-methyl-2-pentanone | −4.145 | −3.550 | −3.233 | −3.683 | −3.618 |
| 2-Methyl-2-pentanol | −4.262 | −2.942 | −1.447 | −1.810 | ∼−1.38 |
| 4-Hydroxy-2-pentanone | −4.317 | −3.668 | −3.013 | | |
| 2-Pentanol | −5.155<br>−5.085 | −3.775 | −1.933 | | |
| *sec*-Butyl alcohol | −5.063<br>−5.003 | −3.525 | −1.755 | | |
| Cyclohexanol | −5.12[b] | −3.928 | −2.228 | −2.470 | |
| 1-Methylcyclohexanol | −4.197 | −2.790 | | −1.743 | −1.317 |

[a] Chemical shifts in p.p.m. relative to TMS as internal standard. [b] Calculated from Humble Oil Company Catalog of NMR Spectra, No. 162.

−2.155 and −2.193 p.p.m., arising from the enol and keto methyls, respectively; (2) the triplet centered at −3.925 p.p.m., arising from HC<; (3) the doublet due to methylene, centered at −2.867 p.p.m.

The peak at −2.155 p.p.m. is assigned to the enol-methyl protons by analogy with the corresponding assignment for acetylacetone.[4]

The fact that only two methyl resonances are observed, rather than one or three, suggests that the following rapid equilibrium exists and that the other nonchelated carbonyls do not participate in the equilibrium.



For the spectra of this compound and the following one, integrated intensities were not available. However, judged from peak heights, the intensities are in good agreement with both assignments.

**B. Compound Melting at 41.5–42.5° (I).**—The n.m.r. data for this compound, together with assignments for the resonances observed, are also given in Table I. There is no line in the region −15 to −17 p.p.m., corresponding to an enolic hydroxyl; nor is there any singlet near −3.0 p.p.m., which could be assigned to a —$CH_2$— attached to two doubly bonded carbon atoms.

The strong singlet at −2.188 p.p.m. agrees well in position with the lines found for the keto methyl groups in acetylacetone, 3-methyl-2,4-pentanedione, and the other 3,5-diacetyl-2,6-heptanedione which melts at 55–56°. These facts indicate this is the tetraketo form.

The triplet at −3.660 p.p.m., which is about 0.265 p.p.m. higher than the corresponding triplet in the monoenol form, is assigned to HC<. The corresponding resonance in the enol form is at lower field because of the carbon–carbon double bond present in the enolic hydroxyl.

In methylene chloride solution the triplet to be expected from the methylene was not observed. The line at −2.348 p.p.m. was considered to be the only line of the methylene triplet which could be observed, the other two lines being buried under the band from the methyl resonance of the keto group. The center of the triplet was estimated to fall at −2.23 p.p.m., and the line at highest field at about −2.13 p.p.m. In Table I these two lines which were hypothesized are in parentheses.

To confirm the existence of this —$CH_2$— triplet, spectra were recorded for the compound in chloroform and thiophene solutions. Table III gives a comparison of the chemical shifts obtained from these spectra. In the thiophene solution the resonance of the acetyl

---

[4] L. W. Reeves, *Can. J. Chem.*, **35**, 1351 (1957).

TABLE III

COMPARISON OF CHEMICAL SHIFTS[a] OF 3,5-DIACETYL-2,6-HEPTANEDIONE, M.P. 41.5–42.5°, IN CHLOROFORM AND THIOPHENE

| Concentration | | | |
|---|---|---|---|
| 21% in $CHCl_3$, 3% TMS, p.p.m. | 20% in thiophene, 3% TMS, p.p.m. | Δ, p.p.m. | Assignment |
| −2.238 | −1.940 | 0.298 | Keto $CH_3$- |
| −2.170 | −2.093 | 0.077 | |
| −2.275 | −2.198 | 0.077 | Triplet $-CH_2-$ |
| −2.383 | −2.308 | 0.075 | |
| | −2.407 | | Impurity |
| −3.593 | −3.403 | 0.190 | |
| −3.700 | −3.512 | 0.188 | Triplet $-\overset{\vert}{\underset{\vert}{C}}H$ |
| −3.812 | −3.623 | 0.189 | |

[a] Relative to TMS as internal standard.

TABLE IV

EFFECT OF INTRAMOLECULAR HYDROGEN BONDING ON METHYL RESONANCE POSITIONS[a] OF $CH_3-\overset{\vert}{\underset{\vert}{C}}-OH$ GROUP

| | | Solvent | | | |
|---|---|---|---|---|---|
| | | $CCl_4$, mole % | | $CH_2Cl_2$, mole % | |
| | Neat | 12.5 | 2.5 | 8.5 | 1.7 |
| 2-Pentanol | −1.128 | −1.078 | −1.065 | | |
| | −1.233 | −1.183 | −1.172 | | |
| | (av., −1.180) | (−1.130) | (−1.118) | | |
| 4-Hydroxy-2-pentanone | −1.093 | −1.097 | −1.065 | | |
| | −1.208 | −1.205 | −1.170 | | |
| | (av., −1.150) | (−1.150) | (−1.117) | | |
| 2-Methyl-2-pentanol | −1.142 | −1.137 | −1.158 | −1.152 | −1.165 |
| 4-Hydroxy-4-methyl-2-pentanone | −1.238 | −1.192 | −1.158 | −1.208 | −1.227 |

[a] Chemical shifts in p.p.m. relative to TMS as internal standard.

group has been shifted far enough upfield so that the triplet of the methylene can be seen.

**Spectra of Compounds with Hydrogen Bonding.**—To aid in the assignment of the spectrum of 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone, the position of the hydroxyl resonance was determined in ten model compounds both neat (with 3% TMS added) and in various solvents in concentrations of, roughly, 15 and 3 w./v. % The actual concentrations in the methylene chloride solutions were 8.5 and 1.7 mole %, and in the carbon tetrachloride solutions, 12.5 and 2.5 mole %. These concentrations correspond to those used for the 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone.

The acetyl resonance positions were also measured in the model compounds and in 2-pentanone and 4-methyl-2-pentanone. In addition, the 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone itself was examined in several solvents at various concentrations.

The model compounds were chosen to cover four groups: (1) β-diketones, (2) *o*-hydroxyphenyl ketones, (3) alcohols, and (4) β-hydroxy ketones. The results are given in Tables II, IV, and V. For ease of comparison, the alcohols have been placed next to the β-hydroxy ketones to which they correspond.

1. Compounds forming conjugated chelates show the following characteristics. (a) For β-diketones, the hydroxyl resonance is between −15.0 and −16.7 p.p.m.; for an *o*-hydroxyphenyl ketone, it is about −12 p.p.m. (b) Both classes show very little change in chemical shift of the hydroxyl resonance when the concentration is changed from 8.5 to 1.7 mole %.

2. Compounds forming intermolecular hydrogen bonds (alcohols) show the following characteristics. (a) The hydroxyl resonance position is at about −4.2 to −5.0 p.p.m. (b) When the compounds are diluted from the pure state to 12.5 mole % in carbon tetrachloride, the chemical shift changed about 1.2 to 1.5 p.p.m.

3. Compounds forming intramolecular hydrogen bonds show the following characteristics. (a) For β-hydroxy ketones, the marked lowering of the position of the hydroxyl resonance found in the β-diketones and the β-hydroxylphenyl ketone does not occur, the chemical shift being very nearly the same as for the corresponding pure alcohols. (b) When the neat β-hydroxy ketones are diluted with carbon tetrachloride, the change in chemical shift for a 12.5 mole % solution is about half as large as the change for the corresponding alcohols.

TABLE V

EFFECT OF INTRAMOLECULAR HYDROGEN BONDING ON ACETYL RESONANCE POSITIONS[a]

| | | Solvent | | | |
|---|---|---|---|---|---|
| | | $CCl_4$, mole % | | $CH_2Cl_2$, mole % | |
| | Neat | 12.5 | 2.5 | 8.5 | 1.7 |
| 2-Pentanone | −2.037 | −2.097 | −2.098 | | |
| 4-Hydroxy-2-pentanone | −2.108 | −2.168 | −2.130 | | |
| 4-Methyl-2-pentanone | −2.117 | −2.088 | −2.060 | −2.073 | −2.058 |
| 4-Hydroxy-4-methyl-2-pentanone | −2.225 | −2.123 | −2.122 | −2.153 | −2.147 |

[a] Chemical shifts in p.p.m. relative to TMS as internal standard.

**Spectrum of 4,6-Diacetyl-3-hydroxy-3-methylcyclohexanone (V).**—The method of preparation indicated

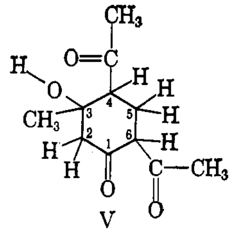

V

TABLE VI

RESONANCE POSITIONS[a] OF 4,6-DIACETYL-3-HYDROXY-3-METHYLCYCLOHEXANONE IN VARIOUS SOLVENTS

| | Concentration | | | | | |
|---|---|---|---|---|---|---|
| Band | 20% in $CH_2Cl_2$, 3% TMS | 20% in $CH_3CN$, 4% TMS | 4% in $CH_2Cl_2$, 3% TMS | 4% in $CCl_4$, 3% TMS | 20% in $CH_3CN$, 4% TMS, 5% $D_2O$ | 20% in $CH_3CN$, 4% TMS, 20% $D_2O$; 0.3% HCl |
| A | −1.255 | −1.215 | −1.257 | −1.223 | −1.240 | −1.265 |
| B | −2.127 | −2.113 | −2.130 | −2.092 | −2.135 | −2.143 |
| C | −2.293 | −2.243 | −2.292 | −2.253 | −2.260 | −2.278 |
| D | −2.367 | −2.348 | −2.372 | Shoulder | −2.372 | −2.407 |
| E | −2.583 | −2.585 | −2.577 | −2.532 | −2.597 | −2.605 |
| F | −3.522 | −3.412 | −3.473 | −3.222 | −3.743 | None |
| G | −15.840 | −15.888 | Not measured | −15.690 | −15.865 | None |
| New band | | | | | −2.798 | −4.443 |

[a] Chemical shifts in p.p.m. relative to TMS as internal standard.

TABLE VII

BAND ASSIGNMENT FOR 4,6-DIACETYL-3-HYDROXY-3-METHYLCYCLOHEXANONE[a]

| Band | Chemical shift, p.p.m. | Relative areas | Structure | Assignment |
|---|---|---|---|---|
| A | −1.255 | $\sim$3 | Singlet | $CH_3$ at C-3 |
| B | −2.127 | $\sim$3 | Singlet | $CH_3CO$ at C-6 |
| C | −2.293 | $\sim$3 | Singlet | $CH_3CO$ at C-4 |
| D | −2.367 | $\sim$2 | Singlet | $CH_2$ at 2 |
| E | $\sim$−2.58 | $\sim$3 | ABC | $CH_2$ at 5<br>CH at 4 |
| F | −3.522 | $\sim$1 | Triplet | OH at C-3 |
| G | −15.840 | $\sim$1 | Singlet | OH on ethylidene |

[a] 20% in $CH_2Cl_2$, 3% TMS.

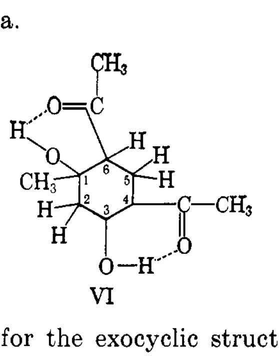
that this substance was 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone.[1]

Although several stereoisomers are possible which may have different axial and equatorial conformations, the sharpness of the melting point indicates the presence of only one. We cannot tell from the spectrum which it is.

The resonance positions for the n.m.r. spectrum of the compound in different solvents at various concentrations are given in Table VI, and a summary of the band assignments in Table VII. A summary of the acetyl and enol methyl resonance positions in a number of compounds is given in Table VIII for comparison.

The per cent of the keto form (structure V) present was determined from the relative areas of bands A, F, and G of Table VII. In a freshly prepared 20% methylene chloride solution, about 20% of the compound is in the keto form. Comparison of the areas of these bands, made on spectra recorded each day for several days after sample preparation, shows that at equilibrium the keto form approaches 10%. Since we used mainly 20% solutions for measuring the spectra, the contribution of the keto form would be negligible. The interpretation of the spectra will therefore be made in terms of the major portion (80–90%) of the compound.

Our data are compatible with either a 4-acetyl-3-hydroxy-6-(1-hydroxyethylidene)-3-methylcyclohexanone structure (III) or a 4,6-diacetyl-1-methyl-3-cyclohexene-1,3-diol structure (VI). Since there seems to be a slight preponderance of evidence in favor of III, we shall discuss the spectrum in terms of it, although we recognize that resonance forms and intramolecular hydrogen bonds diminish both the differences between III and VI and the differences one would expect in the n.m.r. spectra.



VI

The evidence for the exocyclic structure, III, is as follows. Examination of the first six compounds in Table VIII shows that the acetyl resonance positions vary from −2.285 to −2.158 p.p.m., while the enol methyl resonance positions vary from −2.155 to −2.000 p.p.m. From this it appears that 2-acetylcyclohexanone has an enol methyl and an exocyclic double bond at C-2. The groups in the 1- and 6-positions in 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone and the corresponding groups in 2-acetylcyclohexanone are very similar. The fact that one of the acetyls of the former falls in the acetyl methyl region, while the other falls in the enol methyl region, leads us to believe that the compound has the exocyclic structure with an enol methyl. The compound appears to be, then, a 1-hydroxyethylidene ketone, quite analogous to the hydroxymethylene ketones which Wheland discusses.[5]

The reasons for the assignments of the various resonance positions will be evident mainly from the data in Tables VI–VIII. However, the following points should also be noted.

The assignment of the "singlet" at −2.367 p.p.m. (D-band) to the protons on C-2 is made by analogy with 2-acetylcyclohexanone, where the resonance of the corresponding protons falls at −2.300 p.p.m., in 20% solution in methylene chloride. This line is relatively broader than the three lines corresponding to the methyls, indicating some unresolved fine structure. Part of the broadening is from spin–spin splitting of the resonance of the protons on C-2 by the hydroxyl proton at C-3. Additional broadening would result if the rate of inversion of the cyclohexane ring is slowed enough by the bulky side groups to produce a slight nonequivalence of the axial and equatorial protons.

The multiplet designated E, which is overlapped on the high-field side by band D, seems to have about fifteen lines. It is probably an ABC spectrum arising from the protons at C-4 and C-5 in structure III.

---

(5) G. W. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, pp. 685–687.

TABLE VIII
ACETYL AND ENOL METHYL RESONANCE POSITIONS[a]

| | | | | Solvent | |
|---|---|---|---|---|---|
| | Acetyl | Enol | State | $CCl_4$, mole % | $CH_2Cl_2$, mole % |
| Methyl isopropenyl ketone | −2.268 | | Neat | | |
| 3-Acetyl-3-penten-2-one | −2.285 | | Neat | | |
| | −2.225 | | | | |
| 3,5-Diacetyl-2,6-heptanedione, m.p. 41.5–42.5° | −2.188 | | | | 8.5 |
| 3,5-Diacetyl-2,6-heptanedione, m.p. 55–56° | −2.193 | −2.155 | | | 8.5 |
| | −2.170 | −2.130 | | | 2.9 |
| 3-Methyl-2,4-pentanedione | −2.162 | −2.092 | Neat | | |
| | −2.160 | −2.093 | | | 7.7 |
| | −2.158 | −2.120 | | | 1.6 |
| Acetylacetone | −2.170 | −2.000 | Neat | | |
| 2-Acetylcyclohexanone | | −2.092 | | | 8.5 |
| | | −2.062 | | | 1.7 |
| | | −2.043 | | 2.5 | |
| 4,6-Diacetyl-3-hydroxy-3-methylcyclohexanone | −2.293 | −2.128 | | | 5.6 |
| | −2.292 | −2.130 | | | 2.1 |
| | −2.253 | −2.092 | | 2.5 | |

[a] Chemical shifts in p.p.m. relative to TMS as internal standard.

The spectra of the compounds containing a hydrogen-bonded hydroxyl group indicate that the region −2.50 to −4.17 p.p.m. is the likely region for the hydrogen-bonded hydroxyl group formed by the hydroxyl at C-3 and the acetyl at C-4. The variation in position of the F-band in different solvents (Table VI) indicates that it is the hydroxyl at C-3. This was confirmed by deuteration carried out in a 20% solution of the compound in acetonitrile, both with and without catalyst (Table VI).

The new band at −2.798 p.p.m. which appeared with $D_2O$ in acetonitrile solution in the absence of a catalyst is probably due to HOD. The new band appearing at −4.443 p.p.m. with $D_2O$ in acetonitrile containing HCl as a catalyst is probably a hydroxyl resonance representing an average from the rapid exchange between HOD and the protons of the F- and G-bands.[6]

The triplet structure of the F-band in methylene chloride, which initially has a separation of 1.3 c.p.s., disappears gradually over a period of 2 weeks. During this time its position does not shift within the limits of the experimental error of our measurements. The rounded contour of the F-band after the disappearance of the fine structure is characteristic of bands in which there is fairly rapid proton exchange.[6] This led to the hypothesis that the change in band contour was due to the formation of hydrochloric acid from the methylene chloride, which catalyzes the proton exchange. A similar loss of fine structure with amines dissolved in chloroform has been observed.[7] Our hypothesis is strengthened by the fact that the irreversible disappearance of fine structure is greatly accelerated when the solution is heated or when HCl fumes are blown over the end of the sample tube.

That the triplet structure of this band is due to spin–spin coupling has been shown by measurements made at 40 Mc./sec.[8] The average of eleven determinations gives a splitting of 1.3 c.p.s., the band being symmetrical.

Since there are no protons on C-3, spin–spin splitting would have to be long range. Davis, *et al.*,[9] have reported long-range spin–spin coupling of H–H and H–F involving more than three consecutive single bonds. Holmes and Kivelson[10] have reported long-range coupling in acetone involving four σ-bonds. Coupling over four or more bonds, where at least one is unsaturated, has also been discovered.[11]

Spin–spin coupling of the protons of a methoxy group to ring protons through five bonds including part of a π-electron system has been reported by Forsen.[12] The magnitude of the coupling constant appears to depend on the exact conformation of the molecule. Similar long-range spin–spin coupling of an OH proton with a ring proton through five bonds, part of which involve π-electrons has been reported by Freeman.[13]

The determination of the protons which may be involved in long-range coupling with the hydroxyl proton on C-3 in the present case is complicated by the fact that the spin–spin splitting characteristic of the F-band is not found elsewhere in the spectrum. The most likely possibility appears to be long-range coupling through four σ-type bonds with the two protons on C-2. Equivalent or nearly equivalent coupling with each of these protons would account for the fact that the F-

---

[6] J. D. Roberts, "Nuclear Magnetic Resonance. Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 63–65.

[7] Professor David J. Wilson, University of Rochester, private communication.

[8] For these measurements, we are indebted to Dr. Wilson Goodlet and Mrs. Evelyn Simon, Tennessee Eastman Co., Kingsport, Tenn.

[9] D. R. Davis, R. P. Lutz, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 246 (1961).

[10] J. R. Holmes and D. Kivelson, *ibid.*, **83**, 2959 (1961).

[11] (a) E. B. Whipple, J. H. Goldstein, and W. E. Stewart, *ibid.*, **81**, 4761 (1959); (b) E. B. Whipple, J. H. Goldstein, and L. Mandell, *J. Chem. Phys.*, **30**, 1109 (1959); (c) R. R. Fraser, *Can. J. Chem.*, **38**, 549 (1960).

[12] S. Forsen, *J. Phys. Chem.*, **67**, 1740 (1963).

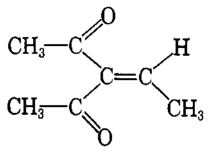
[13] R. Freeman, *Mol. Phys.*, **6**, 535 (1963).

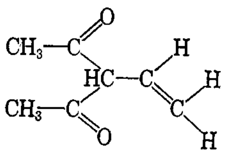
band appears to be a symmetrical triplet. This spin–spin coupling would also explain the greater width of the D-band which we have assigned to the protons on C-2.

The structure on the F-band was clearly shown to be due to spin–spin coupling of the hydroxyl proton with the protons on C-2 by the application of "double resonance" methods.[14] When the F-band resonance was observed while the protons corresponding to the D-band were strongly irradiated, the fine structure of the F-band was removed and it became a single sharp peak. Conversely, when the D-band resonance was observed while the proton corresponding to the F-band was strongly irradiated, the D-band became somewhat sharper and its amplitude increased. These experiments establish that the protons corresponding to the D- and F-bands are spin–spin coupled.

Our interpretation of the spectrum of this substance on the basis that it is 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone is also in agreement with infrared data[15] showing two carbonyl bands, one at 1690 which could be characteristic of carbonyl in a $\beta$-hydroxy ketone, and the other at 1600 cm.$^{-1}$ which could occur only in a conjugated chelate.[3] An intense hydroxyl band at 3420 cm.$^{-1}$, characteristic of a $\beta$-hydroxy ketone, and a not very well defined band in the 2700–2500-cm.$^{-1}$ region, characteristic of the hydroxyl in a conjugated chelate, were also observed. These spectra were obtained both in KBr pellets and in methylene chloride solution.

**Spectrum of 3-Acetyl-3-penten-2-one (3-Ethylidene-2,4-pentanedione).**—The method of preparation of this compound 2,4-pentanedione and acetaldehyde[1] suggests either the 3-acetyl-3-penten-2-one (VII) or the 3-acetyl-4-penten-2-one structure (VIII).


VII


VIII

The resonance positions for the n.m.r. bands of the pure compound (with 3% TMS as internal reference) are given in Table IX. No band which could be ascribed to a vinyl group,[16] even as an impurity of 1–2%, was seen.

TABLE IX

CHEMICAL SHIFTS[a] AND SPIN–SPIN COUPLING CONSTANTS FOR 3-ACETYL-3-PENTEN-2-ONE

| P.p.m. | Band contour | Relative intensities | $J_{H,CH_3}$, c.p.s. | Assignment |
|---|---|---|---|---|
| −1.848 | Doublet | 3 | 7.2 | $CH_3—C=C$ |
| −2.225 | Singlet | 3 | | Methyl at C-1′ |
| −2.285 | Singlet | 3 | | Methyl at C-1 |
| −6.915 | Quartet | 1 | 7.4 | $=\underset{\vert}{C}H$ |

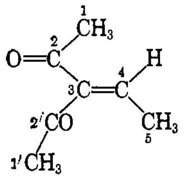
[a] Chemical shifts in p.p.m. relative to TMS as internal standard.

The quartet and doublet with the same fine structure splitting, and the magnitude of this, 7.2–7.4 c.p.s., show conclusively that there are a *sib*[17] proton and a methyl group. The chemical shifts for these two groups also agree well with those for an ethylenic hydrogen and for a methyl attached to doubly bonded carbon.[11,18] The relative intensities of these two resonances are in the ratio 1:3. These features identify the compound as the ethylidene, rather than the vinyl, pentanedione.

The two singlets at −2.225 and −2.285 p.p.m. have been assigned to the methyls of the two acetyl groups. From both areas and peak heights, it is known that each corresponds to three hydrogens.

In the infrared region (smear on NaCl), two carbonyl bands, one at 1700 and the other at 1660 cm.$^{-1}$, are observed.[15] The latter is in the region characteristic of $\alpha,\beta$-unsaturated ketones,[19] whereas the former is close to the region for saturated, open-chain ketones.[19a]

These n.m.r. and infrared data are consistent with the following hypothesis as to the conformation of the molecule. Fisher–Taylor–Hirschfelder and Courtauld models show a severe steric hindrance between the *gem*-diacetyls, which is not present between the *gem*-diacetyl groups of the heptanediones previously discussed. According to the models, conformation IX gives the least steric hindrance. In this conformation the carbonyl at C-2 is coplanar with the ethylenic carbons, whereas that at C-2′ is out of this plane.


IX

The carbonyl at C-2 then would have the frequency 1660 cm.$^{-1}$, agreeing with the broad carbonyl band at 1670–1660 cm.$^{-1}$ reported for *trans*-3-penten-2-one.[19b,c] The carbonyl at C-2′, which is out of the plane and therefore not conjugated, would have the frequency at 1700 cm.$^{-1}$.

Two effects cause the proton resonance of the methyl attached to the more conjugated carbonyl to occur at a lower field than that of the methyl attached at C-1′. The first is the greater electron withdrawal associated with the more conjugated carbonyl. The second is the fact that the model shows this methyl to be situated quite close to the transverse axis of the carbon–carbon

---

[14] L. F. Johnson, Varian Associates Publication No. 87-100-082, Palo Alto, Calif., August, 1962.

[15] For these measurements and for assistance with the interpretation, we are indebted to Miss Thelma Davis of these laboratories.

[16] (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 238-241; (b) R. W. Fessenden and J. S. Waugh, *J. Chem. Phys.*, **30**, 944 (1959).

[17] The term "*sib*" is proposed to describe a group which is attached to a given atom, but which differs in structure from the other groups attached to the same atom. The use of "*gem*" for this is etymologically unsound, since the Latin root of *gem* means twin, and is contrary to the accepted usage of *gem* in such phrases as "the *gem*-dimethyl grouping in camphor."

[18] (a) L. M. Jackman and R. H. Wiley, *Proc. Chem. Soc.*, 196 (1958); in the last line of the 2nd paragraph, read "*trans*" for "*cis*." (b) J. A. Elvidge, *J. Chem. Soc.*, 474 (1959).

[19] (a) Ref. 3b, pp. 132, 136; (b) R. Heilmann, D. de Gaudemaris, and P. Arnaud, *Compt. rend.*, **240**, 1995 (1955); (c) R. Heilmann, G. de Gaudemaris, and P. Arnaud, *Bull. soc. chim. France*, 119 (1957).

double bond. It will therefore be subjected to a negative (deshielding) effect from the anisotropy of this bond.[20] The resonance at −2.285 p.p.m. is therefore assigned to the methyl at C-1 and that at −2.225 p.p.m. to the methyl at C-1′.

Our ultraviolet spectral data in methanol solution agree with those of McEntee and Pinder.[21]

---

[20] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 124, 129.

[21] M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, 4419 (1957).

---

# Preparation of 1-Azabicycloalkanes by Reductive Cyclization

MANFRED G. REINECKE[1a] AND LOUIS R. KRAY[1b]

*Department of Chemistry, University of California, Riverside, California*

*Received November 29, 1963*

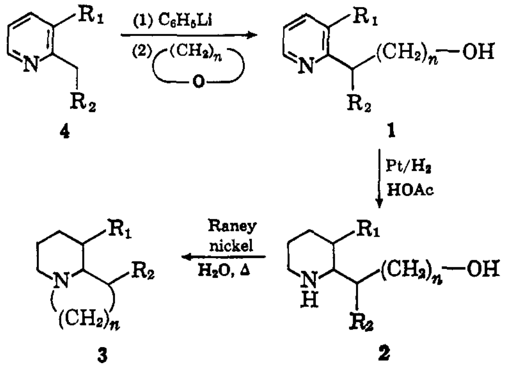
Indolizidine, quinolizidine, and several of their methyl derivatives have been prepared in 80–90% yield by the two-step reductive cyclization of readily available 2-pyridyl alcohols. Under similar conditions, the corresponding 3- and 4-pyridyl alcohols failed to undergo cyclization. The probable stereochemistry of the 8-methylindolizidines produced in this cyclization is discussed.

In connection with another problem in this laboratory we recently required substantial quantities of various indolizidines and quinolizidines. Although several methods for synthesizing compounds of this type had been reported in the literature,[2] for the most part these proceeded in low over-all yields from readily available starting materials. The most attractive method in this regard seemed to be the high-pressure, high-temperature, reductive cyclization of various 2-(3′-hydroxypropyl)pyridines such as **1a** to the corresponding indolizidines. In the case of indolizidine itself (**3a**) a 78% yield was reported[3] although with slightly more complex molecules it was much lower.[4] Repeated attempts to prepare indolizidine by this method in our laboratory, however, led only to complex mixtures containing, at best, 15% of the desired product.[5]

A related method which was considered was that of Lavagnino, *et al.*,[6] in which indolizidine (**3a**) was obtained in 73% yield by simply distilling an aqueous solution of 2-(3′-hydroxypropyl)piperidine (**2a**) from Raney nickel. Since the piperidine **2a** is easily prepared by catalytic reduction[3] of the commercially available pyridine **1a**, it appeared that this sequence of two reactions (reduction followed by cyclization) might be used for the preparation of the desired compounds. This paper reports the synthesis of a variety of indolizidines and quinolizidines in 80–90% over-all yield by this two-step reductive cyclization of readily available pyridyl alcohols of the type **1**.

## Results and Discussion

The starting pyridyl alcohols **1** were obtained either commercially (**1a**), or by treatment of the appropriate alkylpyridyllithium reagent[7] with ethylene oxide[8] (**1c, 1e–g**) or propylene oxide[9] (**1b** and **1d**). Reduction of the pyridine ring of **1a–g** proceeded in 92–96% yield at room temperature and moderate pressure according to the method of Prelog.[10] The saturated alcohols **2a–g** produced in this reaction were partially esterified by the glacial acetic acid used as a solvent and therefore were saponified before isolation and purification. In those preparations where only the final quinolizidines or indolizidines were desired, the crude mixture of piperidyl alcohols **2a–g** and their acetate esters could be used without prior saponification since hydrolysis apparently took place under the conditions of the cyclization described below.



Cyclization of the piperidyl alcohols **2a–g** to the desired indolizidines and quinolizidines **3a–g** took place in high yield (85–95%) by a procedure very similar to that of Lavagnino, *et al.*[6] The 15% higher yields in our cyclizations may be due to the repeated use of the same portion of Raney nickel, since the ability of the catalyst to irreversibly adsorb either the reactants or the products[11] would be greatly reduced after the first prep-

---

[1] (a) Department of Chemistry, Texas Christian University, Fort Worth, Texas; (b) National Science Foundation Summer Teaching Fellow, 1963; National Institutes of Health Predoctoral Fellow in Chemistry, 1963–1964.

[2] For a recent summary of the syntheses of compounds with bridgehead nitrogen atoms, see W. L. Mosby, "The Chemistry of Heterocyclic Compounds," Vol. 15, parts 1 and 2, A. Weissburger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961.

[3] V. Boekelheide and S. Rothchild, *J. Am. Chem. Soc.*, **70**, 864 (1948).

[4] J. Sam, J. Plampin, and D. Alwani, *J. Org. Chem.*, **27**, 4543 (1962).

[5] The reason for the failure of this synthesis in our hands is not clear, although the exact nature of the Raney nickel catalyst used may be responsible. The identities of the products obtained from this attempted reductive cyclization are under investigation and will be reported elsewhere.

[6] E. R. Lavagnino, R. R. Chauvette, W. N. Cannon, and E. C. Kornfeld, *J. Am. Chem. Soc.*, **82**, 2609 (1960).

[7] The successful preparation of at least a 25% yield (see Table I) of the lithium reagent of 2-isopropylpyridine is surprising in view of the failure of C. Osuch and R. Levine [*J. Org. Chem.*, **21**, 1099 (1956)] and W. von E. Doering and V. Z. Pasternak [*J. Am. Chem. Soc.*, **72**, 143 (1950)] to metalate 2-isopropyl- and 2-*sec*-butylpyridine, respectively, with phenyllithum under essentially identical conditions (see Experimental).

[8] L. A. Walter, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 757.

[9] K. Winterfeld and W. Haring, *Arch. Pharm.*, **295**, 615 (1962).

[10] V. Prelog and O. Metzler, *Helv. Chim. Acta*, **29**, 1163 (1946).

[11] For examples of the irreversible adsorption of certain amines on Raney nickel, see (a) A. Bendich, P. Russell, Jr., and J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954); and (b) M. G. Reinecke and L. R. Kray, unpublished results.