SECTION I: SYNTHESES OF POLYHYDROAZAPHENANTHRENES

SECTION II: CHEMISTRY OF POLYHYDROINDANONES

By

Gary H. Rasmusson

B. A., St. Olaf College

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Signature of Author ______________________
Department of Chemistry
May 25, 1962

Certified by ______________________
Thesis Supervisor

Accepted by ______________________
Chairman
Department Committee on Graduate Students.

This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Prof. George Buchi (Chairman) ____________________

Prof. Herbert O. House (Thesis Supervisor) ____________________

Prof. Arthur C. Cope ____________________

Prof. John S. Waugh ____________________

Prof. Dietmar Seyferth ____________________

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ABSTRACT

SECTION I: SYNTHESES OF POLYHYDROAZAPHENANTHRENES

a) Stobbe condensation with 6-methoxy-1-tetralone followed by cyclization and decarbethoxylation afforded the dihydrobenzindanone VI. This material was reduced and carried through a Beckmann rearrangement. to give the octahydroazaphenanthrone IXa.

b) Micheal addition of methyl acrylate to 2-tetralone afforded a keto-ester. The oxime of this material was reduced to give the octahydroazaphenanthrone IXb.

SECTION II: CHEMISTRY OF POLYHYDROINDANONES

a) Diels-Alder reaction of 4-cyclopentene-1, 3-dione with butadiene gave a tetrahydroindanedione whose enol ether was converted into 3-vinyl-3a, 4, 7, 7a-tetrahydroindenone (VII) by reaction with vinylmagnesium chloride and hydrolysis. Diels-Alder reaction of VII with acrylic acid gave the octahydrofluorenone X. The use of 2, 4-pentadienoic acid and its methyl ester as dienes in Diels-Alder reactions has been investigated.

b) The Diels-Alder reactions of butadiene and of trans 1, 3-pentadiene with cyclopentenone have been studied. The products, 3a, 4, 7, 7a-tetrahydroindanone and 7-methyl-3a, 4, 7, 7a-tetrahydroindanone, and the corresponding hexahydroindanones have been equilibrated in triethylamine. The per cent of the trans isomers at equilibrium for hexahydroindanone, 3a, 4, 7, 7a-tetrahydroindanone, 7-methylhexahydroindanone and 7-methyl-3a, 4, 7, 7a-tetrahydroindanone were respectively 25, 47. 5, 75 and 99%.

c) The synthesis of α-methyl-α, β-unsaturated esters by the Wittig reaction has been found to be stereoselective.

d) Cyclopentane-1, 2-dione underwent Micheal addition with methyl vinyl ketone to give 1-(2, 3-dioxocyclopentyl)-3-butanone.

Thesis Supervisor
Title: Associate Professor of Chemistry.

DEDICATED TO MY WIFE, NANCY.

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SECTION I

SYNTHESES OF POLYHYDROAZAPHENANTHRENES

INTRODUCTION

Heterocyclic compounds containing nitrogen receive much attention from the biological and medicinal chemist because of their universal occurrence and application in physiological systems. This attention certainly has not gone without reward as evidenced by the multitude of aza-heterocyclic compounds now being used in various areas of medicine. Synthetic drugs which have found wide application as a class include the barbiturates used as hypnotics and anticonvulsants, phenothiazines as tranquillizers and quinoline derivatives as antimalarials. The naturally occurring alkaloids are aza-heterocyclic compounds, many of which have pronounced physiological action. The biological action of such compounds is almost certainly due in part to the presence of the nitrogen atom in the molecule. Present theories regard a nitrogen atom as being very important in the binding of such molecules to enzyme systems, thus, enhancing or abating the associated physiological action.

Fully aromatic azaphenanthrenes[1] have been found in several cases physiologically active. The medicinal Diapurin which causes increased uric acid excretion is 3-phenylbenzo(f)quinoline-1-carboxylic acid.[2] Many aza-

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1) A recent review of azaphenanthrene chemistry may be found in "The Chemistry of Heterocyclic Compounds," Vol. 12, C. H. F. Allen, ed., "Six-membered Heterocyclic Nitrogen Compounds with Three Condensed Rings". Interscience Publishers, Inc., New York, N. Y., 1958, p. 165 f.

2) A. Levi, Biochim. e terapia sper., 10, 59-83 (1923); C.A., 17, 3718 (1923).

phenanthrenes have been screened with some success as antimalarials.[3]

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[3] F. Y. Wiseloge, "Survey of Anti-malarial Drugs." Vol. II, J. E. Edwards, Ann Arbor, Mich., 1946, pp. 1310-1321.

Nitrosubstituted azaphenanthrenes cause central paralysis and temperature drop in mammalian systems.[4] Several other azaphenanthrenes have been

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[4] B. Kindt and H. Vollmer, Arch. Exptl. Path. u. Pharmakol., 148, 198 (1930); C.A., 24, 2803 (1930).

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found to be biologically active as antibacterials,[5] typanocidal agents[6] or as

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[5] (a) I. G. Farbenindustrie A. -G., Br. Pat. 282, 143, Sept. 11, 1926; C. A., 22, 3735 (1928).
(b) P. Karrer and A. Pletscher, Helv. Chim. Acta, 31, 786 (1948).

[6] (a) R. E. Haworth and W. O. Sykes, J. Chem. Soc., 311 (1944).
(b) G. Morgan, L. Walls, C. Browning, R. Gulbransen and J. Robb, J. Chem. Soc., 389 (1938).

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other therapeutic agents.[7]

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[7] (a) R. L. Evans, U.S. Pat. 2,518,130, Aug. 8, 1950; C.A., 45, 1169 (1951).
(b) W. A. Petrow, J. Chem. Soc., 200 (1946).

Polyhydroazaphenanthrenes, with the exception of lysergic acid derivatives, have been studied relatively little with respect to their syntheses and biological activity. They are also of interest because they may be used as precursors for nitrogen analogs of steroids. Little is known of the biological effects which might occur as a result of the incorporation of a nitrogen atom in a steroid molecule. An azasteroid would be expected to have the same dimensions as its parent molecule and, thus, should be able to react with the same enzyme systems. The presence of the nitrogen atom may even give the azasteroid a specific or enhanced effect.

A suitable precursor for such a system may be 1, 2, 3, 4, 4a, 5, 6, 10b-octahydro-3-oxo-8-methoxybenzo(f)quinoline (I). This molecule contains essential groups at the 3-, 13- and 14-positions which might be elaborated further to furnish an 14-azasteroid derivative related to the estrogens, such as the aza-doisynolic acid derivative II. Doisynolic acid itself is a potent estrogen derived from estrone.[8]

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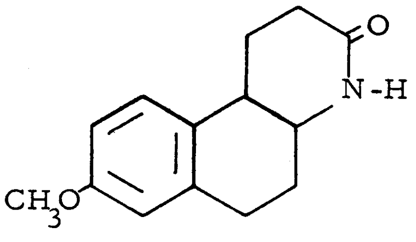
[8] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 494.



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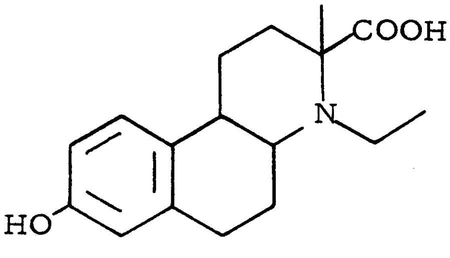

II

Tetrahydroazaphenanthrenes in which the hetero-ring is reduced may be easily attained by reduction of the corresponding azaphenanthrene. Further reduction of the molecule leads primarily to the ar-octahydro compound of type III.[9] Thus, a molecule in which adjacent aliphatic rings are desired must be approached synthetically in a different manner. It was desired to do this by fusing the hetero-ring to the appropriately reduced naphthalene system.

PART I

2-Methoxynaphthalene served as a convenient starting material. Reduction of this material over Raney nickel catalyst afforded 6-methoxy-1, 2, 3, 4-tetrahydronaphthalene[10] in about 90% yield. Oxidation of the tetrahydro compound with chromic acid gave 6-methoxy-1-tetralone[11] (IV) in 43% yield. This material was converted to 1-carbethoxy-2, 3a, 4, 5-tetrahydro-7-methoxy-3-benz(e)indone (V) by Stobbe condensation followed by cyclization with zinc chloride in acetic anhydride. Compound V could not be isolated pure and had to be characterized as its semicarbazone. Decarbethoxylation of the keto-ester V in aqueous hydrochloric acid afforded 4, 5-dihydro-7-

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[9] E. Bamberger and R. Muller, Ber. 24, 2653 (1891).

[10] G. Stork, J. Am. Chem. Soc., 69, 576 (1947).

[11] (a) V. Burnop, G. Elliot and R. Linstead, J. Chem. Soc., 727 (1940).
(b) E. Schwenk and D. Papa, J. Am. Chem. Soc., 67, 1432 (1945).

methoxy-3-benz(e)indanone (VI) in 43.7% yield (based on 6-methoxy-1-tetralone). This material had been prepared by Birch and co-workers on a small scale.[12]

Attempts to catalytically reduce the unsaturated ketone VI led only to non-ketonic products. This is not entirely unexpected for a tetrasubstituted double bond conjugated with an aromatic ring and a ketone function. Reduction with sodium in liquid ammonia, however, gave the saturated cyclopentanone[13] VII in high yield.[14] The ring junction was tentatively assigned the *cis* configuration on the basis that it should be most stable. Linstead and Quinkert in their reviews[15] on such systems indicated that the *cis* isomer of 1-hydrindanone is much more stable than the *trans* isomer. Molecular models of the *cis* compound are much less strained than those of the corre- *trans* compound. Equilibration studies have shown that the most stable compound is formed in the reduction.[14] This would be expected since in the workup from a basic medium the enolate must be in equilibrium with the ketone.

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12) A. J. Birch, J. Quartey and H. Smith, J. Chem. Soc., 1768 (1952).

13) J. C. Wollensak, Ph.D. Thesis, Massachusetts Institute of Technology, 93 (1958).

14) N. Nelson, J. Wollensak, R. Foltz, J. Hester, Jr., J. Brauman, R. Garland and G. Rasmusson, J. Am. Chem. Soc., **82**, 2569 (1960).

15) (a) R. P. Linstead, Ann. Repts., **32**, 305 (1935).
(b) G. Quinkert, Experientia, **13**, 381 (1957).

Nevertheless, it has been shown[16] that with 2, 3-disubstituted indenones, when reduced with lithium in ammonia and decomposed in aqueous ammonium chloride, the predominant isomer is the *cis* 2, 3-disubstituted indanone. Thus, the *cis* isomer would appear to be favored both on a kinetic and on a thermodynamic basis. Also, studies in the steroid field on similar tetrahydroindanones have shown that the *cis* isomer is the more stable.[17]

Reaction of the ketone VII with hydroxylamine hydrochloride in pyridine-methanol afforded the oxime in fair yield. Although both isomers of the oxime were probably present,[18] it is presumed that the *syn* isomer VIII would predominate as there would be steric interaction between the hydroxylimino group and the atoms of the central ring in the case of the *anti* isomer. In α-disubstituted hydroxylimines this steric interaction is presumably so large that the *syn* isomer is formed almost exclusively.[19]

Beckmann rearrangement of the oxime in the presence of dioxane and thionyl chloride afforded the corresponding lactam, formulated as IXa, in 50% yield. As the Beckmann rearrangement proceeds with retention of

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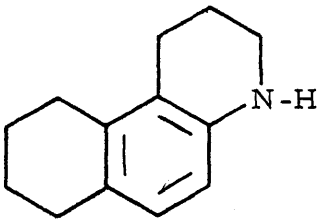
[16] H. E. Zimmerman, J. Am. Chem. Soc., *78*, 1168 (1956).

[17] A. S. Dreiding, Chemistry and Industry, 992 (1954).

[18] S. Hara, Pharm. Bull. (Japan), *3*, 209 (1955).

[19] B. Regan and F. Hayes, J. Am. Chem. Soc., *78*, 639 (1956), and references therein.



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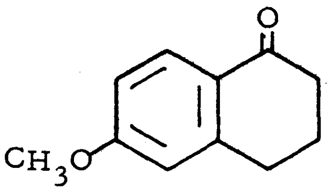

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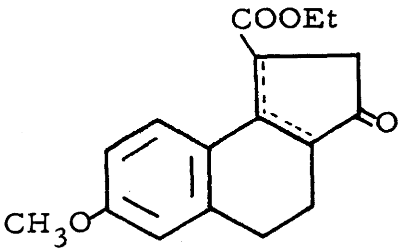

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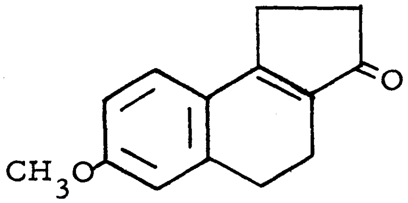

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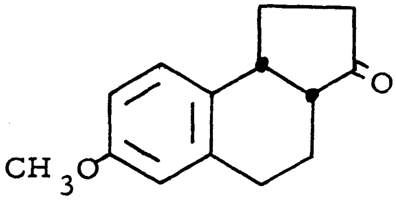

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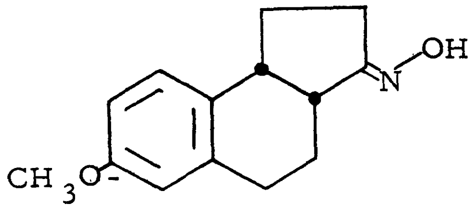
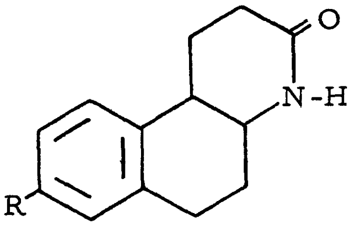
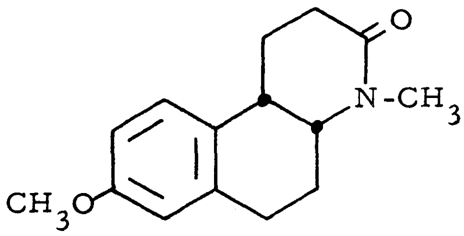


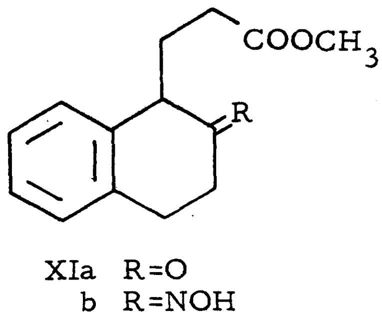
VIII



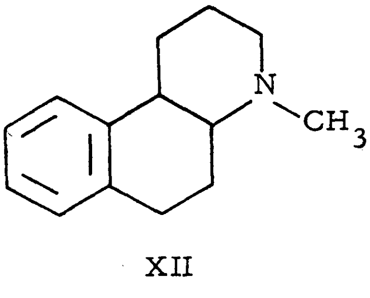
IXa R-OCH$_3$
b R-H



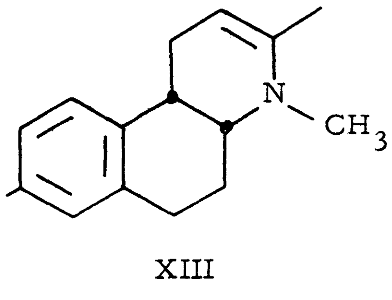
X



XIa R=O
b R=NOH



XII



XIII

configuration of the migrating group[20] the B-C ring juncture would probably remain *cis.* This method has become very common in the preparation of aliphatic azaheterocycles and is seen frequently in the preparation of aza-steroid derivatives.[18, 19, 21] The rearrangement proceeded normally as was shown by the infrared spectrum which showed both lactam carbonyl (1655 cm.$^{-1}$) and hydrogen-nitrogen (3195 cm.$^{-1}$ and 3390 cm.$^{-1}$) absorption.

Treatment of this lactam with sodium hydride followed by methyl iodide afforded the N-methyl compound X in good yield. The method used was that of Gates and Tschudi[22] where the N-alkyl product was the only one observed. In agreement with this, compound X showed no nitrogen-hydrogen absorption in the infrared spectrum.

An attempt was made to study the reaction of methyl magnesium iodide with X with the hope of obtaining the enamine XIII. This type of reaction has been observed by Lukes and Malek.[23] In several attempts, however,

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[20] A. Campbell and J. Kenyon, J. Chem. Soc., 25 (1946).

[21] (a) K. Tsuda and R. Hayatsu, J. Am. Chem. Soc., 78, 1380 (1956).
(b) H. Heusser, J. Wohlfarhdt, M. Muller and R. Anliker, Helv. Chim. Acta, 38, 926 (1955).
(c) St. Kaufmann, J. Am. Chem. Soc., 73, 1779 (1951).
(d) C. W. Shoppee and J. C. P. Sly, J. Chem. Soc., 3458 (1958).
(e) R. H. Mazur, J. Am. Chem. Soc., 81, 1454 (1959).

[22] M. Gates and G. Tschudi, J. Am. Chem. Soc., 78, 1380 (1956).

[23] R. Lukes and J. Malek, Chem. Listy, 45, 72 (1951); C.A., 9523 (1951).

only starting material could be recovered. The failure of these experiments may have been due to the instability of the organo-metallic in the presence of methyl iodide in tetrahydrofuran.[24] Additional material and time were not available to further this study, however. Addition of hydrogen cyanide to XIII or reaction of the corresponding perchlorate compound with cyanide ion[25] would have been expected to afford a nitrile of the corresponding aza-derivative (II) of doisynolic acid.

PART II

As a second approach to the octahydroazaphenanthrene system a different method of ring formation was desired such that it might be possible to arrive at the trans configuration between the two aliphatic rings. A likely possibility was to be found in the ring closure of an amine with an appropriately positioned ester group.

β-Tetralone, which is readily obtainable from β-naphthol,[26] served as a convenient starting material. This substance when treated with an equal molar quantity of methyl acrylate in dilute sodium methoxide afforded a Micheal addition product XI in moderate yield (37%). Addition of acrylonitrile

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24) H. Gilman and B. Gaj, J. Org. Chem., 22, 1165 (1957).

25) N. J. Leonard, R. W. Fulmer and A. S. Hay, J. Am. Chem. Soc., 78, 3462 (1956).

26) A. J. Birch, J. Chem. Soc., 431 (1944).

to β-tetralone has been reported recently by Russian workers[27] in about the same yield. Compound XI was characterized as its semicarbazone.

1-(β-Carbomethoxyethyl)-2-tetralone (XIa) was converted to its oxime (XIb) in fair yield (60%). This material when reduced in acetic acid gave the lactam IXb directly in good yield. A similar reductive ring closure has been observed by Bolt.[28] The configuration of the ring juncture is not known. N-Methylation followed by lithium aluminum hydride reduction of this lactam would afford a compound (XII) that could be compared with a compound[29] which presumably has the *cis* configuration.

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27) N. P. Shusherina, R. Ya. Levina and V. I. Zdanovich, Zhur. Obshchei Khim., 26, 2847-51 (1956).

28) C. C. Bolt, Rec. trav. chim., 57, 905 (1938).

29) R. S. P. Hsi, Ph.D. Thesis, Massachusetts Institute of Technology, 1959, p. 15.

EXPERIMENTAL[30]

6-Methoxy-1, 2, 3, 4-tetrahydronaphthalene. - This material was prepared according to the procedure of Stork.[10] 2-Methoxynaphthalene (485 g., 3.07 moles) was dissolved in 90 ml. of ethanol and hydrogenated in the presence of Raney nickel catalyst (W-2)[31] at an initial pressure of 1800 psi and 80° to give 456.3 g. (92.5%) of 6-methoxy-1, 2, 3, 4-tetrahydronaphthalene, b.p. 125.5-127.5° (14 mm.). Vapor phase chromatography indicated that greater than 90% of the isolated material was the desired tetralin.

6-Methoxy-1-tetralone. - 6-Methoxy-1, 2, 3, 4-tetrahydronaphthalene (454 g., 2.82 moles) was oxidized[11] with chromic acid to give 268.1 g. (54%) of 6-methoxy-1-tetralone, b.p. 171-181° (14 mm.). Recrystallization from benzene-hexane gave 211.9 g. (42.6%) of white crystalline material, m.p. 77-79° (lit.[11a] m.p. 77.5°).

4, 5-Dihydro-7-methoxy-3-benz(e)indanone (VI).[12] - To a solution of potassium *t*-butoxide, prepared from dried *t*-butyl alcohol (200 ml.) and potassium metal (8.2 g., 0.21 mole), was added 6-methoxy-1-tetralone

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[30] Melting points and boiling points are uncorrected. The infrared spectra were determined with a Perkin-Elmer, model 21, infrared recording spectrophotometer with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates.

[31] R. Mozingo, Org. Syntheses, Coll. Vol. 3, 181 (1955).

(35. 2 g., 0. 20 mole) and diethyl succinate (52 g., 0. 28 mole). The system was then evacuated and filled with nitrogen. The mixture was refluxed for 90 min. and then allowed to cool to room temperature. The mixture was then acidified by addition of 40 ml. of 20% hydrochloric acid and was concentrated under reduced pressure. Water was added to the residue and the resulting mixture was extracted thoroughly with ether. The ethereal layers were combined and extracted with 1 N ammonium hydroxide solution until a test portion gave no precipitate upon acidification. The alkaline extract was washed once with ether and was then added slowly to a slight excess of cold dilute hydrochloric acid with stirring. The Stobbe condensation half-ester separated as a deep red oil which was then extracted into ether, dried over magnesium sulfate, and reconcentrated to the oil (38. 6 g.), which exhibits infrared absorption[32] at 1700-1740 cm.$^{-1}$ (acid and ester carbonyls). This material was used in the next step without further purification.

To a solution of the crude Stobbe condensation product (38. 6 g.) in 600 ml. of acetic anhydride was added 300 ml. of acetic acid containing 1. 50 g. of freshly fused zinc chloride. The mixture was refluxed for 1. 5 hr. and then allowed to stand at room temperature overnight. Water (165 ml.) was added with caution to the cooled mixture, followed by addition of 385 ml. of 20% hydrochloric acid. The mixture was reluxed until carbon-dioxide evolution ceased. It was then concentrated under reduced pressure to a dark oil which was treated with 200 ml. of 4% sodium carbonate solution and ex-

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32) Determined as a solution in chloroform.

tracted with ether. The ether extract was dried over magnesium sulfate and concentrated to a brown semicrystalline material. This material was passed through 800 g. of acid washed alumina using benzene and benzene-ether as eluents. The ketone obtained by this method was relatively pure, m.p. 95-97° (14.17 g., 43.7% yield based on recovered 6-methoxytetralone, 7.5 g.). Recrystallization from benzene-petroleum ether gave a white, finely crystalline material, m.p. 96.5-97.5° (lit. m.p. 96-97°),[12] which exhibits infrared absorption[33] at 1690 (cyclopentenone carbonyl) and 1040 cm.$^{-1}$ (methyl ether), and has ultraviolet absorption[34] at 239 (ϵ 12,600) and 328 mμ (ϵ 23,700).

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33) Determined as a solution in carbontetrachloride.
34) Determined as a solution in 95% ethanol.

<u>1-Carbethoxy-2,3a,4,5-tetrahydro-7-methoxy-3-benz(e)indenone (V) semicarbazone.</u> - The crude Stobbe condensation product (10.4 g.), obtained as shown above, was dissolved in 180 ml. of acetic anhydride and 90 ml. of acetic acid and was combined with 90 ml. of acetic acid containing 1.0 g. of freshly fused zinc chloride. The mixture was then refluxed under nitrogen for 3.25 hr. The reaction mixture was then chilled and the excess acetic anhydride was destroyed by cautious addition of 80 ml. of water. The mixture was concentrated under reduced pressures to a red-brown oil which was taken up in ether, washed with 250-ml. portions of 8% sodium bicarbonate solution and with water. The ether layer was dried and concentrated to a tan oil. This oil was combined with 100 ml. of absolute ethanol, 8 ml. of pyridine and 9.5 g. of semicarbazide hydrochloride and heated 45 min. at 70-76°. The solution was diluted with an equal amount of water and filtered, yielding

a yellow semicarbazone (6.65 g.), m.p. 215-218°, (d., inserted at 205°). Recrystallization from ethanol-chloroform gave a white solid, m.p. 223° (d., inserted at 215°), which was light sensitive; it exhibited infrared absorption[35] at 3460 (N-H), 1720 (unsaturated ester), and 1680 cm.$^{-1}$ (semicarbazone carbonyl).

Anal. Calcd. for $C_{18}H_{21}N_3O_4$: C, 62.97; H, 6.17. Found: C, 62.86; H, 6.32.

Decomposition of the semicarbazone (0.50 g., 0.0015 mole) in 50 ml. of 20% hydrochloric acid at 100° afforded the unsaturated ketone VI (0.096 g., 31%), m.p. 95.5-97°. However, decomposition of the semicarbazone (39.5 g., 0.115 mole) in relatively less 20% hydrochloric acid (1200 ml.) afforded none of the expected material, but only a lusterous deep red material (35 g.), m.p. 248-250° (d). This material was only slightly soluble in ether, chloroform, acetone, and other organic solvents. Recrystallization from dioxane-ethanol gave a dull red powder, m.p. 254°, inserted at 250°.

Anal. Found: C, 72.75; H, 6.51; N, 6.18.

This material shows general absorption[34] in the ultraviolet spectrum with distinct maxima at 260 and 333 mμ. The infrared spectrum has no absorption in the region for carbonyls but has infrared absorption[35] at 1250 (methyl-phenyl ether), 1138, 1400 and 1580 cm.$^{-1}$.

3a, 4, 5, 9b-Tetrahydro-6-methoxy-3-benz(e)indanone (VII). - Com-

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35) Determined as a suspension in potassium bromide.

mercial ammonia was purified by distillation from a sodium solution to the dried reaction vessel. Sodium (0.754 g., 0.033 mole) was added to the distilled ammonia (ca. 350 ml.), followed by addition of an ether solution of the unsaturated ketone (3.22 g., 0.015 mole). The reaction mixture was stirred for an additional 30 min., the solution turning deep green in color. Excess ammonium chloride was then added and the solution became colorless. The ammonia was distilled under a stream of nitrogen. When the solution reached room temperature more ether was added. The ether solution was washed with ca. 125 ml. of water, dried over magnesium sulfate and concentrated to a pale yellow oil which readily crystallized. Recrystallization from petroleum ether (b.p. 30-60°) afforded 3.05 g. (94%) of the saturated ketone, m.p. 64-65°, which shows infrared absorption[33] at 1735 (cyclopentanone carbonyl) and 1045 cm.$^{-1}$ (methyl ether). This material gave no depression in melting point with a sample prepared by a different route.[13]

syn-3a,4,5,9b-Tetrahydro-6-methoxy-3-benz(e)indanone oxime (VIII). - The saturated ketone (3.00 g., 0.0139 mole), hydroxylamine hydrochloride (2.66 g., 0.039 mole), pyridine (5.42 g., 0.07 mole) and 15 ml. of methanol were combined and stirred at room temperature for 18.5 hr. Water (200 ml.) containing 5 ml. of concentrated hydrochloric acid was then added to the reaction mixture which was then immediately extracted with ether. The ethereal layer was dried over magnesium sulfate and concentrated to a pale yellow oil which solidified slowly. Recrystallization from cyclohexane yielded 2.3 g. of the oxime, m.p. 101-110°. A second recrystallization from aqueous methanol gave 1.78 g. of the white oxime, m.p. 112-115°. An analytically pure sample had m. p. 119-120.5°; infrared absorption[32] at 3580 and 3240 (hydroxyl group), and 1670 cm.$^{-1}$ (weak, carbon-nitrogen double bond).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.89; H, 7.46; N, 6.08.

1, 2, 3, 4, 4a, 5, 6, 10b-Octahydro-3-oxo-8-methoxybenzo(f)quinoline (IXa). - A solution of 3.00 g. (0.013 mole) of the crude oxime (m.p. 108-113°) in 100 ml. of purified dioxane was cooled with stirring to 14°. A solution of thionyl chloride (8.3 g., 0.07 mole) in 30 ml. of purified dioxane was added dropwise at such a rate that the temperature of the reaction mixture did not rise above 16°. After complete addition the mixture (orange) was stirred for an additional 15 min. A concentrated solution of potassium carbonate was then added to the mixture at such a rate that the temperature did not rise above 20°. When carbon-dioxide evolution ceased, the dioxane solution was decanted from the inorganic salt, which in turn was washed with chloroform. The combined dioxane-chloroform solution was concentrated at reduced pressure to a brown semi-solid. Solution of this material in chloroform, followed by drying over magnesium sulfate and concentration yielded a crystalline brown solid. Recrystallization from ethyl acetate afforded 1.51 g. (50%) of the crystalline, white lactam, m.p. 157-158°. An additional recrystallization raised the melting point to 159-159.5°; the infrared spectrum[32] of this material has maxima at 3375 and 3190 (nitrogen-hydrogen), 1655 (lactam carbonyl) and 1043 cm.$^{-1}$ (methyl ether).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.40; N, 6.06. Found: C, 72.46; H, 7.21; N, 6.40.

1, 2, 3, 4, 4a, 5, 6, 10b-Octahydro-3-oxo-4-methyl-8-methoxybenzo-(f)quinoline (X). - A solution of the lactam (1.55 g., 0.0067 mole) in 350 ml. of dried toluene was distilled until *ca.* 50 ml. of solvent had been removed. Sodium hydride (0.195 g., 0.008 mole) was added and the mixture refluxed for 3.5 hr. It was then cooled (gelatinous suspension) and 10 ml. of chilled methyl iodide was added. Refluxing was resumed for 1 hr. The cooled, cloudy mixture was treated with about 130 ml. of water. The toluene layer was separated and the aqueous layer treated once with *ca.* 200 ml. of toluene. The combined toluene layers were dried over magnesium sulfate and evaporated under reduced pressure to a pale yellow solid (1.8 g.). Recrystallization of this material from ethyl acetate afforded 1.25 g. (77%) of the white, crystalline lactam, m.p. 163.5-164.5°, depresses starting material melting point to 138-146°, which has infrared absorption[32] at 1620 (lactam carbonyl) and 1045 cm.$^{-1}$ (methyl ether), no N-H absorption above 3000 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.68; H, 7.70; N, 5.57.

1-(β-Carbomethoxyethyl)-2-tetralone. - Sodium (0.75 g., 0.0325 mole) was added to 300 ml. of absolute methanol. The sodium methoxide solution was then cooled to 0° and β-tetralone[26] (53.69 g., 0.366 mole) was added with stirring. With continued cooling and stirring methyl acrylate (31.5 g., 0.366 mole) was added slowly over a period of 45 min. The solution was then stirred for 3 hr. while the solution temperature was gradually allowed to come to room temperature. The solution was neutralized with aqueous hydrochloric acid and the mixture concentrated under reduced pressure to a pink oil. The oil was taken up in ether, dried over magnesium sulfate and reconcentrated. The resulting oil was distilled at reduced pressure through a 36-cm. Vigreaux column. The distillation afforded 19.66 g. of unchanged tetralone (b.p. 91-97° at 7 mm.) and 20.05 g. (37%) of the mono-adduct XIa (b.p. 176-182° at 6.0 mm.) along with higher boiling residues which did not distill. The keto-ester was characterized as its semicarbazone which was prepared by heating the crude Micheal addition product (1.14 g., 0.0049 mole) with semicarbazide hydrochloride (1.5 g., 0.013 mole) and 1.0 ml. of pyridine in 10 ml. of absolute methanol for 45 min. on a steam bath. The hot reaction mixture was then treated with water until it became cloudy. The semicarbazone (1.20 g., 85%) separated on cooling, m.p. 146-150°. Further recrystallizations from aqueous ethanol and from ethyl acetate afforded pure 1-(β-carbomethoxyethyl)-2-tetralone semicarbazone, m.p. 161° which has infrared absorption[32] at 1730 (ester carbonyl), 1685 (semicarbazone carbonyl), 3420 and 3220 cm.$^{-1}$ (nitrogen-hydrogen stretching).

Anal. Calcd. for $C_{15}H_{19}N_3O_3$: C, 62.16; H, 6.62; N, 14.52. Found: C, 62.22; H, 6.57; N, 14.44.

1-(β-Carbomethoxyethyl)-2-tetralone oxime (XIb). - The crude keto-ester (1.0 g., 0.0043 mole) was combined with hydroxylamine hydrochloride (0.91 g., 0.013 mole), pyridine (1.9 g., 0.0215 mole) and 5 ml. of absolute methanol and was allowed to stand at room temperature for 30 hr. The mixture was then treated with 70 ml. of water containing 1.9 ml. of concentrated hydrochloric acid and extracted immediately into ether. Concentration of the dried ether layer yielded a yellow solid. Recrystallization of this material from cyclohexane after decolorization with Norit afforded 650 mg. (61%) of a white solid, m.p. 91-96°. Additional recrystallizations from benzene-petroleum ether (b.p. 30-60°) and from cyclohexane gave 320 mg. of a white compound, m.p. 99.5-101.0°, which has infrared absorption[32] at 3630 and 3280 (oxygen-hydrogen stretching) and 1730 cm.$^{-1}$ (ester carbonyl).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.67. Found: C, 68.31; H, 6.96; N, 5.74.

1,2,3,4,4a,5,6,10b-Octahydro-3-oxo-benzo(f)quinoline (XII). - The above oximino-ester (0.85 g., 0.0034 mole) was dissolved in 40 ml. of acetic acid containing 0.090 g. of platinum oxide catalyst. This mixture was stirred under hydrogen at atmospheric pressure until the theoretical uptake of hydrogen occurred. The catalyst was removed and the solution was concentrated at reduced pressure. The residual tan oil was treated with aqueous potassium carbonate and then extracted into chloroform. The chloroform layer was concentrated under reduced pressure to an oil which readily solidified. Washing of the solid with ether left 0.48 g. (72%) of the white crystalline lactam, m.p. 178-180°. An analytical sample had m.p. 183°, sharp, infrared absorption[32] at 3380 and 3180 (amide hydrogen) and 1655 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 77.57; H, 7.52; N, 6.96. Found: C, 77.46; H, 7.22; N, 7.03.

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SECTION II

CHEMISTRY OF POLYHYDROINDANONES

HISTORICAL REVIEW

HISTORICAL REVIEW

Syntheses of Polyhydro-1-indanones

Polyhydro-1-indanones have received much study in the field of organic chemistry because of their wide-spread occurrence in natural products of biological and chemical interest. The synthesis of this ring system has, thus, been a necessary prerequisite in the synthetic attack on the more complex molecules. As a result, many synthetic routes have been developed for these condensed 5-6 ring ketones. Some of these methods are discussed below.

One may conveniently prepare 4, 5, 6, 7-tetrahydroindanone (IIa) from the cyclohexanone Stobbe condensation product Ia by acid catalyzed ring closure followed by decarbethoxylation.[1] Other methods which have been used with some degree of success include various acid catalyzed ring closures of the following compounds: Ib[2] and its acid chloride,[3] vinyl cyclohexenyl ketone,[4] the Mannich base III,[5] octahydrocoumarin[6] and the Mannich base IV.[7] The latter reaction is a modification of a discovery by Nazarov.

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He found that vinyl cyclohexenyl acetylenes are hydrolyzed and cyclized in a phosphoric-formic acid mixture to give the 3-methyltetrahydroindanone IIb.[8] When cyclohexene is allowed to react with crotonaldehyde in polyphosphoric acid[9] or with β-chlorobutyrylchloride in the presence of aluminum chloride,[10] the 3-methyltetrahydroindanone IIb is formed in moderate yield.

Diels-Alder reactions with cyclopentenone should afford 3a, 4, 7, 7a-tetrahydroindanones, but this reaction has received only moderate investigation. The reaction of butadiene with cyclopentenone has been reported,[11] but the product of the reaction, Va, which was obtained in low yield, could only be characterized as its dinitrophenylhydrazone. The only other active study in this area has been Diels-Alder reactions with the more readily available 2, 4-dimethyl-2-cyclopentenone.[12] In this case, to obtain even moderate yields of the product Vb a large excess of the ketone over the diene

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was necessary, thus, making this method of little synthetic value. 2,3-Dimethylbutadiene has been used to prepare the compound VI, which by further transformations has been converted into the tetrahydroindanone VII.[13] Reaction of 1-acetoxybutadiene with 3-methyl-3-cyclopenten-1,2-dione gave the product VIII which was of interest in the synthesis of vitamin D_3.[14]

The parent compounds corresponding to 5,6,7,7a-; 3a,4,5,7a-; 3a,6,7,7a- and 3a,4,5,6-tetrahydroindanones are unknown although the 3a,6,7,7a-tetrahydroindanone system IX is present in the steroid equilenin and the 3a,4,5,6-tetrahydroindanone system X has been found in degradation products of steroids.[15]

Hexahydroindanones have been obtained by catalytic reduction of tetrahydroindanones prepared as described above or by appropriate manipulation of 1,2-disubstituted cyclohexane derivatives. The first preparation of hydrindanone (XI) was accomplished by pyrolysis of the anhydride derived from o-carboxyperhydrocinnamic acid (XIIIa).[16] The existence of

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two isomers of hydrindanone was discovered later when fractional crystallization of the oxime benzoate derivatives afforded *cis* and *trans* isomers corresponding to XIa and XIb.[17] Since this early work most of the experimental investigations on the synthesis of these ring systems has been in the stereospecific formation of one of these isomers. As the hydrindanone ring system present in the steroids' C-D rings is *trans* and contains a methyl group at the bridgehead carbon adjacent to the carbonyl, it has been desirable to synthesize the *trans* 7a-methylhydrindanone (XIIb) as a model compound in the total synthesis of steroids. As a rule, the precursor to this system has been the diacid XIIIb or its esters, for in this system the stereochemistry at the ring junction is fixed before cyclization. The more straightforward method of making XII by methylation of the hydrindanone XIV affords predominately the *cis* isomer XIIa.[18] To make matters even more difficult, conventional routes to the diacid XIIIb at best give a mixture of *cis* and *trans* isomers.[19] It was only with considerable difficulty that the *trans* hydrindanone

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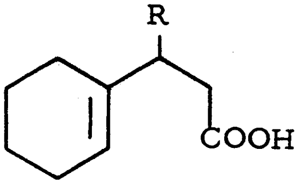
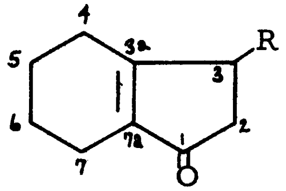
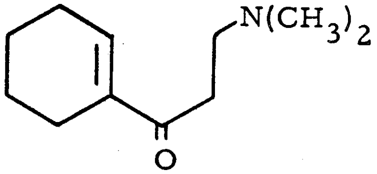


Ia R=$COOC_2H_5$
b R=H



IIa R=H
b R=CH_3



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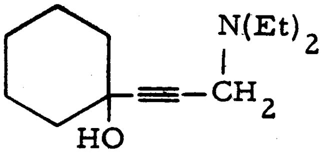
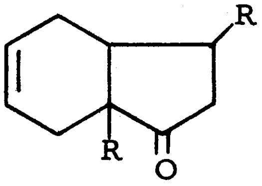
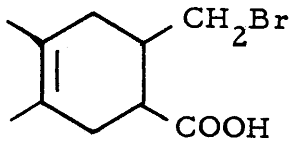


IV



Va R=H
b R=CH_3



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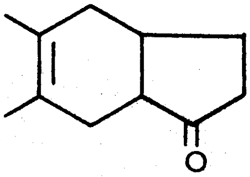

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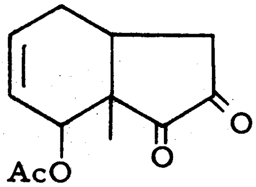
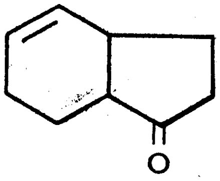
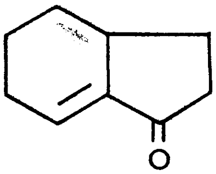


VIII

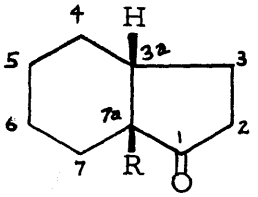


IX



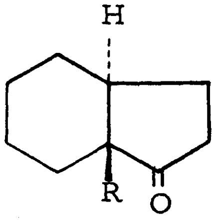
X

XIIb could be synthesized with complete stereospecificity.[20] The fact that the *trans* octalone XVb results as the primary product from methylation of XVa has simplified the total synthesis of estrone.[21] The diester XVI can be made to undergo an acyloin condensation which after reduction and dehydration affords a convenient synthesis of the hydrindanone XII in good yield.[22] This method was also used with considerable success in a total synthesis of estrone.[23]



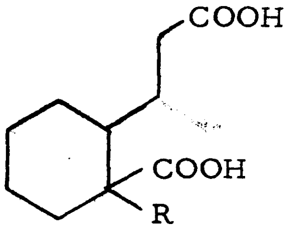
XIa R=H

XIIa R=CH_3



XIb R=H

XIIb R=CH_3



XIIIa R=H

b R=CH_3

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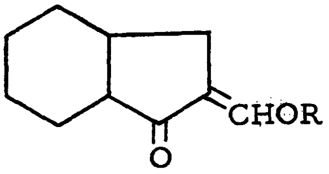
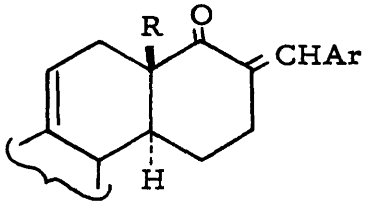
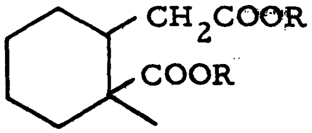

XIV


XVa R=H
b R=CH_3


XVI

Stability Relationships of Polyhydroindanones[24]

Calculated energy differences between cis and trans isomers in decalin systems correspond very well with empirical values.[25] Extension of these calculations to hydrindane systems results in very poor correlation with experimental results.[17b, 26] The added factor of ring strain introduced by the cyclopentane ring must be the prime reason for the hydrindane systems' anomalous behavior. An examination of a molecular model of the trans hydrindane system shows that in order to accomodate the five-membered ring, the six-membered ring must adopt a more extreme chair conformation, thus, accentuating 1, 3-diaxial interactions and causing the system to be quite rigid. The cis isomer, on the other hand, tends to open up the chair

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25) (a) R. B. Turner, J. Am. Chem. Soc., 74, 2118 (1952).
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26) (a) N. L. Allinger and J. L. Coke, J. Am. Chem. Soc., 82, 2553 (1960).
(b) W. B. Dauben, O. Rohr, A. Laubbauf and F. D. Rossini, J. Phys. Chem., 64, 283 (1960).

conformation, thus reducing diaxial interactions in the six-membered ring. The cis -hydrindane is much more flexible and only suffers energetically from having more gauche-type interactions than does the trans isomer. These effects make the isomeric hydrindanes very close to one another in energy, the trans isomer being of slightly lower energy (i. e., more stable).[17b, 26] Introduction of a bridgehead methyl group reverses the stability such that the cis isomer predominates almost exclusively at equilibrium.[28] This effect is probably due to the additional gauche interactions introduced by the methyl group[13] in the trans compound, thus raising its energy above that of the cis isomer. Similarly, in hydrindanone systems the stability of cis and trans isomers are very close. In 1-hydrindanone the cis isomer is more stable, while in the 2-hydrindanone the trans isomer is the more stable form.[17b] Using the preferred conformation of these simple compounds as a basis, conformational analysis[29] has been used to determine relative stabilities of hydrindanone epimers.[24]

Conformational effects have been used to explain the extent of isomerization of several 1-hydrindanone derivatives derived from steroids.[30]

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28) N. L. Allinger, J. Org. Chem., 21, 915 (1956).

29) (a) D. H. R. Barton and R. C. Cookson, Quart. Revs., 10, 44 (1956).
(b) W. G. Dauben and K. S. Pitzer in M. S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, New York, N. Y., 1956, p. 1.

30) J. F. Bielmann, D. Francetic and G. Ourisson, Tetrahedron Letters, no. 18, 4 (1960).

In all cases the cis isomer predominated, but the amount of this isomer in the equilibrium mixture varied considerably with the structure of the compound. They found that by placing a methyl group at a bridgehead carbon in place of a hydrogen atom it was possible to obtain considerably more of the cis isomer at equilibrium. The reason for this shift in favor of the cis compound is probably due to the destabilization of the trans form by the gauche interaction between the bonds CH_3-C_{3a} and C_1-C_7 in the trans methyl compound (XVII). They found that 1, 3-diaxial interactions of the type shown in XVIII tend to destabilize the cis form by forcing the carbonyl carbon out of the axial position. The cis form is also destabilized to some extent by 1, 3-diaxial interactions which tend to force the carbonyl carbon into a more extreme axial position (i. e., XIX).

Quantitative equilibrium studies have been run on another series of steroidal hydrindanones. In this case also the cis isomer predominated in all cases studied.[31] The rates of equilibration of the ketones were measured and the thermodynamic quantities were calculated. Neglecting 1, 3-nonbonding interactions they derived a theoretical method for calculating the enthalpy of epimerization of hydrindanones by employing the method which worked well in the case of the decalins[29] and decalones.[25] A "perturbation" constant was added in in these calculations for conversion from the one system to the other. The results from use of this theoretical treatment were in fair accord with experimental values and may be of some value in the treatment of

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31) N. L. Allinger, R. B. Hermann and C. Djerassi, J. Org. Chem., 25, 922 (1960).

other hydrindanone systems where non-bonded interactions[30] do not play an important part.

The common conception that all 1-hydrindanones are more stable in the _cis_ form[32] is not true. Barton and Laws have found that the 15-keto cholestanols are more stable in the _trans_ form (XX).[15] The corresponding _cis_ form XXI is probably unfavored because in this situation the geometry of the cyclopentanone ring is such that the alkyl side chain becomes eclipsed with the axial methyl group and serious steric interactions come into play. It is interesting to note that the very similar type of compound XXII exists preferentially as the _cis_ isomer.[33] The reason for this must lie in the fact that compound XXII exists in the conformation XXIIa where the cyclohexanone ring has flipped to give a more stable situation.

Allinger has stated that much of the confusion regarding the stabilities of hydrindanes and hydrindanones has developed because heat content has not been differentiated from free energy.[28] The latter term is a true measure of stability of a system and is a combination of heat content and entropy. In systems such as hydrindanones where the heat contents of the isomers in question lie close together, the entropy difference between the forms may be sufficient to determine which isomer will predominate

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32) A. S. Dreiding, Chemistry and Industry, 992 (1954).

33) (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 216.
(b) K. Dimroth and H. Jonsson, Ber., _74_, 520 (1941).

at equilibrium. Thus, cis hydrindane, which has a higher heat content than the trans isomer, actually predominates in an equilibrium mixture at temperatures above 466°K.[26a] The reason for this is that the cis isomer being more flexible and less symetrical than the trans has a more positive entropy of formation. Conversely, the incorporation of the hydrindanone system into a rigid steroid nucleus should practically eliminate the effect of entropy and should cause the cis isomers to appear less stable than the parent compound. Experimental evidence for this type of behavior is not at hand, although in the quantitative studies carried out on steroidal hydrindanones[30, 31] several systems were closer to a 50-50 mixture at equilibrium than would ordinarily be expected.

No studies have been carried out on the stereochemistry of 3a, 4, 7, 7a-tetrahydroindanones. In one case[13] two semicarbazones of compound VII were isolated which may have been ring cis-trans isomers. The 7a-methyl-3a, 6, 7, 7a-tetrahydroindanone system in equilenin has been equilibrated at 250° in the presence of palladium and has been found to lie predominately on the side of the cis isomer.[34]

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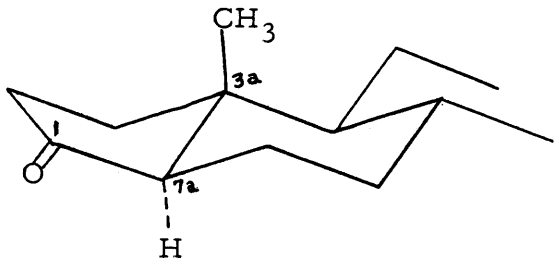
34) W. E. Bachmann and A. S. Dreiding, J. Am. Chem. Soc., 72, 1323 (1950).



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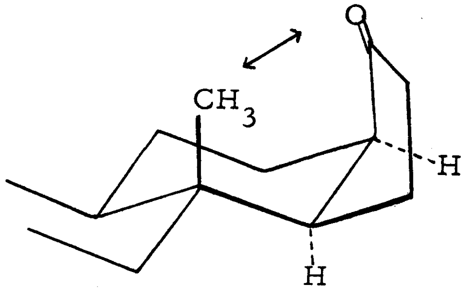

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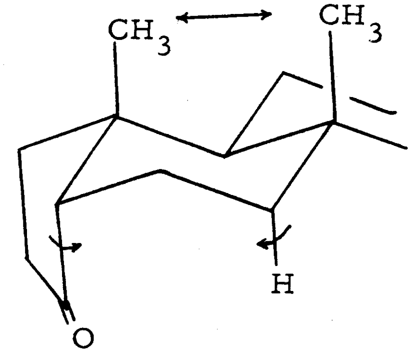

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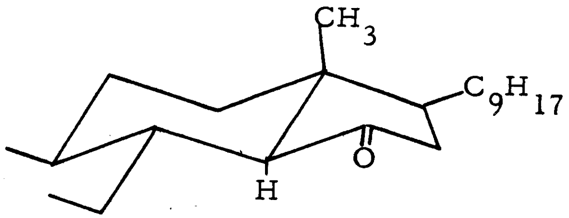

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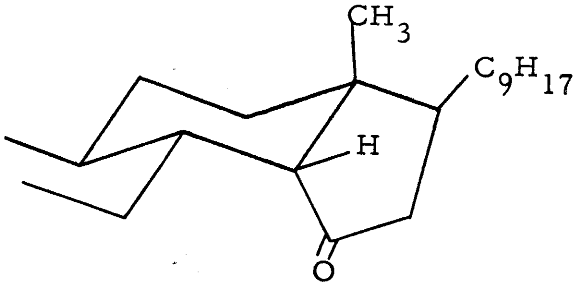

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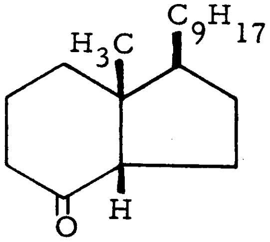

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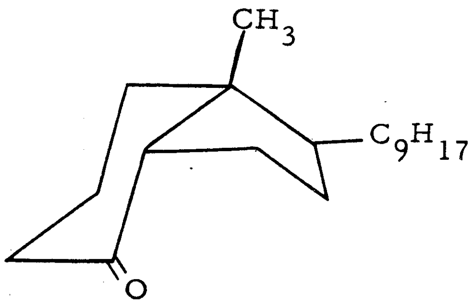

XXIIa

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3) C. D. Nenitzescu and V. Przematzky, Ber., 74B, 676 (1941).

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SECTION II

CHEMISTRY OF POLYHYDROINDANONES

PART I

POLYHYDROINDANONES AS SYNTHETIC INTERMEDIATES

PART ONE: POLYHYDROINDANONES AS SYNTHETIC INTERMEDIATES

It is obvious from the structure of gibberellic acid (I) that the total synthesis of this material or of related gibberellins[1] must at some stage employ the formation and elaboration of a suitably substituted hydrindane derivative. This work was undertaken to study methods of synthesizing functional hydrindanes which might serve as intermediates or as model compounds in the eventual total synthesis of the gibberellins. More exactly, the utility of the Diels-Alder reaction in forming various unsaturated hydrindanone systems was explored to see if this method could be of synthetic value.

The reactive 4-cyclopenten-1,3-dione (II) served as an attractive starting material, not only because it is a reactive dienophile in Diels-Alder reactions,[2] but it also affords a polyfunctional system which may undergo further elaboration. The preparation of this material from the corresponding cyclopentenediols was improved such that a higher yield of the diketone could be obtained. Its use as a synthetic intermediate has been made more practical.[3]

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[1] 1) For a recent review see J. F. Grove, Quart. Revs., 15, 56 (1961).

[2] 2) (a) C. H. DePuy and E. F. Zaweski, J. Am. Chem. Soc., 81, 4920 (1959).
(b) C. H. DePuy and C. E. Lyons, J. Am. Chem. Soc., 82, 631 (1960).

[3] 3) H. O. House, G. H. Rasmusson, C. H. DePuy and E. F. Zaweski, Org. Syntheses, in press.

This diketone reacted smoothly with butadiene and piperylene to afford the corresponding tetrahydroindan-1, 3-diones IIIa and IIIb, respectively. Catalytic reduction of IIIa afforded cis hydrindan-1, 3-dione (IV).[4]

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[4] Since completion of this work the synthesis of this material has been reported by V. F. Kucherov and L. I. Ivanova, Daklady Akad. Nauk, S.S.S.R., 131, 1077 (1960); C.A., 54, 21021b (1960).

Compound IIIa was easily methylated in methanolic hydrogen chloride or with diazomethane to give the enol ether IIIc. Similarly, the cyclopentenedione II could be reduced to the enolic diketone Va[2a] and then converted to the enol ether Vb.

The enol ether IIIc was of interest because it could be envisioned as a model of the B-C ring system found in the gibberellins. Reaction of this material with vinyl magnesium chloride gave the vinyl alcohol VI. Treatment of this material with dilute acid afforded the corresponding dehydration-hydrolysis product VII. Both VI and VII were isolated only as partially purified intermediates because of their tendency to polymerize under normal working conditions. That the diene system in VII was actually present was verified by the fact that the Diels-Alder adduct VIII could be obtained by reaction with N-phenylmaleimide. Similar reaction with acrylic acid afforded two products, one neutral and the other acidic. The neutral material has been assigned structure IX on the basis of its analytical and spectral data.[5] The acidic material has been assigned structure X

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[5] For a detailed account of these data see the experimental section.

and thus would serve as a model system for the A-B-C rings of the gibberellins.

Since very mild reaction conditions were employed in the various Diels-Alder reactions described above, it is very likely that the kinetically controlled product resulted in each case. It is well known[6] that Diels-Alder reactions proceed by *cis*, *endo* addition of the dienophile to the diene. Also, the addition of dienophiles to dienes may be expected to occur from the less hindered side.[6] The stereochemical assignments for the compounds shown are based on these considerations. The Diels-Alder reaction affording X may be envisioned as giving either the 1-carboxy compound shown or the corresponding 2-carboxy isomer. Evidence favoring X is strong as similar Diels-Alder reactions have been found to proceed to give the isomer where the substituents on the end of the diene and of the dienophile are adjacent to one another in the cyclized product.[7] The position of the endocyclic double bonds in IX and X were verified by the ultraviolet and nuclear magnetic resonance spectra.[5] Evidently in the workup of these materials the double bond migrated from the expected 4, 4a-position into the more stable endocyclic position.

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[6] J. G. Martin and R. K. Hill, Chem. Revs., *61*, 537 (1961).

[7] (a) I. N. Nazarov, A. I. Kuznetsova and N. V. Kuznetsov, J. Gen. Chem., U.S.S.R., *25*, 75 (1955).
(b) I. N. Nazarov, *Y.* Titov and A. I. Kuznetsova, Acad. Sci. U.S.S.R., Chem. Sci. Bull., 1224 (1959).
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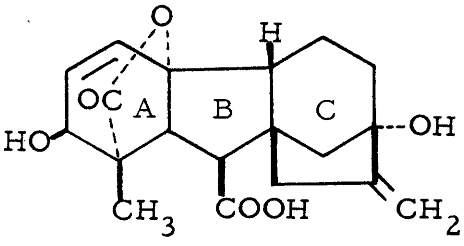
(d) K. Alder, et. al., Ann., *564*, 79 (1949).



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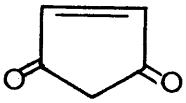

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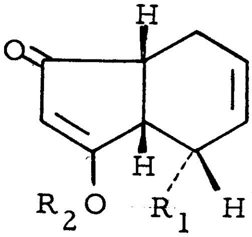
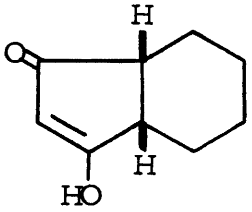


IIIa R_1=H R_2=H

b R_1=CH_3 R_2=H

c R_1=H R_2=CH_3



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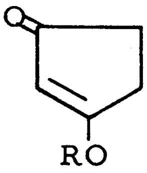
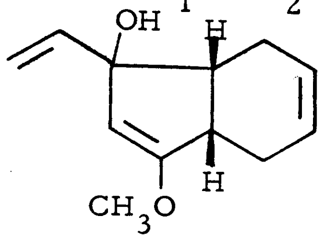


V a R=H

b R=CH_3



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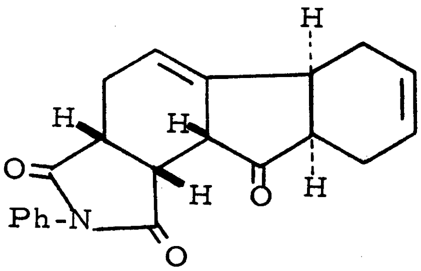

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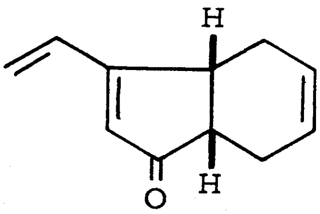
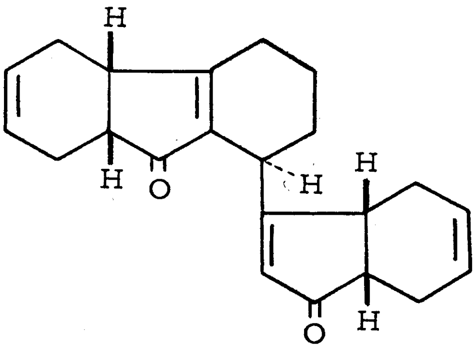


VII



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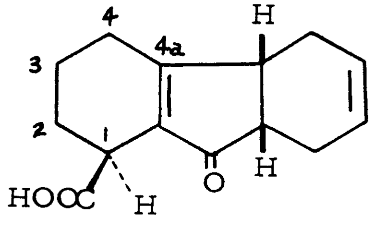

X

This general synthetic approach to the ring system of the gibberellins was considered unattractive because of the instability of the intermediates VI and VII and, particularly, because of the complications involved in the final step (i.e., the low yield of X and the competing side reaction).

Attention was then diverted to another approach to the above type of system utilizing the polyhydroindenone XI. This material was obtained by lithium aluminum hydride reduction of IIIc followed by a hydrolysis step similar to the one used in formation of VII. It is interesting to note that in the hydride reduction inverse addition was necessary to obtain optimum yields of XI.

When this material was heated in the presence of dicyclopentadiene at 175° for two days no Diels-Alder product could be isolated. However, a crude rearranged dienone assigned structure XII could be isolated in 60% yield. The nuclear magnetic spectrum[5] of this material definitely excludes the alternative structure XIII. Other evidence for the dienone structure XII was the catalytic hydrogenation of this material to 4, 5, 6, 7-tetrahydroindanone, XIV.

When the dienone XI was heated at 170° for two days with cyclopentadiene monomer a solid product could be isolated in low yield from a complex mixture of products which included considerable starting material. However, this material retained the cyclopentenone chromophore in its infrared spectrum and could not have been the desired product XV. From the above results it became clear that XI could not be used as a dienophile in a synthetic scheme and further studies in this area were abandoned.

The use of trans-2, 4-pentadienoic acid (XVIa) as a diene in Diels-Alder reactions has been illustrated.[7b] It was of interest to study the Diels-Alder reactions of this compound such that a method might be devised for obtaining derivatives of the 7-carboxyhydrindanone XVII, a model system for the A-B rings of the gibberellins.

When pentadienoic acid, XVIa, or its ester, XVIb, was treated with reactive dienophiles such as N-phenylmalemide or the cyclopentenedione II, the corresponding Diels-Alder adduct (XVIII and XIX) could be isolated. However, when the attempted Diels-Alder reaction of XVIb with cyclopentenone was carried out, none of the desired adduct XVII could be isolated. The only product of this reaction was a material to which is assigned structure XX. This same material was also formed when XVIb was heated in the absence of cyclopentenone. This corresponds to the reported[7c] dimerization of XVIa to the acid lactone XXI. All attempts to isolate an adduct of the diene XXII[8] with any of the dienophiles studied (including tetracyanoethylene) were fruitless. Evidently, the presence of the α-methyl group prevents this compound from assuming the required cisoid conformation necessary for participation in Diels-Alder reaction.[6]

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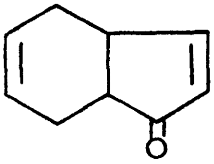
8) The synthesis of this material is described in the Appendix; see also H. O. House and G. H. Rasmusson, J. Org. Chem., 26, 4278 (1961).



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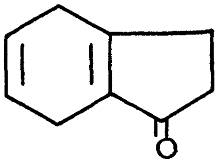

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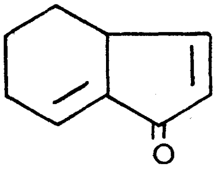

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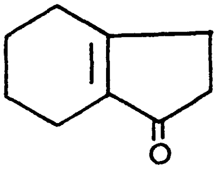

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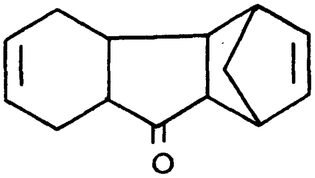

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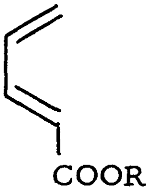
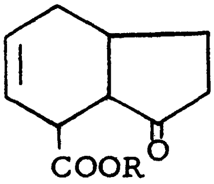


XVI a R=H
b $R=CH_3$



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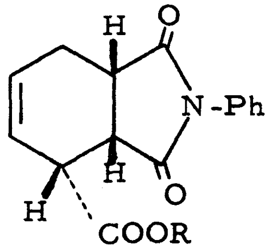
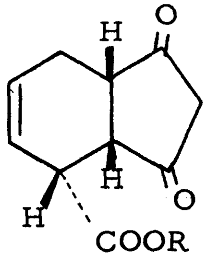
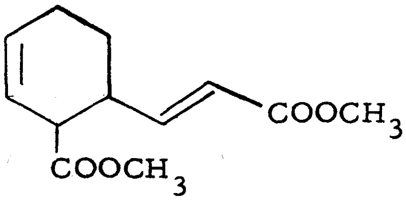


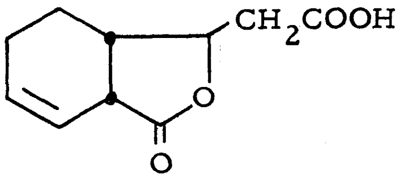
XVIII a R=H
b $R=CH_3$



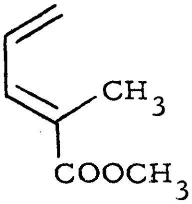
XIX a R=H
b $R=CH_3$



XX



XXI



XXII

EXPERIMENTAL[9]

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[9] All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird, model B, or a Perkin-Elmer, model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. Unless otherwise stated magnesium sulfate was employed as a drying agent. The NMR spectra were determined with a Varian, model A-60, NMR spectrometer.

4-Cyclopenten-1, 3-dione (II).[2] A. From a mixture of cyclopentenediols (Columbia Southern Chemical Co.). This procedure has the advantage of eliminating the sometimes tedious job of isolation of the 1, 3-diols. Oxidation products of the 1, 2-diols are water soluble and do not interfere with the isolation of the desired 1, 3-diketone.

The commercial mixture of diols (45.1 g.) was dissolved in water (200 ml.) and combined with methylene chloride (300 ml.) in a three neck flask fitted with stirrer and dropping funnel. The mixture was then cooled to -5° in a Dry Ice-methanol-water slurry, and 800 ml. of a solution of sulfuric acid (320 ml.) and chromium trioxide (200 g.) in water (900 ml.) was added dropwise at such a rate that the temperature did not rise above 0°. After complete addition of the oxidant, the reaction was stirred at 0° for 1 hr. At this point the mixture still had excess oxidant present as evidenced by a positive test with 0.4% aqueous sodium diphenylamine sulfonate solution. Chloroform (150 ml.) was then added to the mixture and

and the phases were separated. The aqueous phase was extracted again with chloroform (200 ml.). The combined organic extracts were dried over magnesium sulfate and evaporated under reduced pressure to afford 21.4 g. of the yellow solid melting near room temperature and of sufficient purity for subsequent reactions.

B. From 4-cyclopenten-1, 3-diol. The commercial mixture of diols (330 g.) was distilled through a 36 in. spinning-band column at reduced pressure. The desired 4-cyclopenten-1, 3-diols came late in the distillation and boiled at 90-95° at 0.75 mm. (n_D^{25} 1.5000-1.5010). 4-Cyclopenten-1, 3-diol (50.5 g., 0.51 mole) ($n_D^{27.5}$ 1.5001) was dissolved in 200 ml. of water and combined with 300 ml. of methylene chloride in a three-necked flask fitted with a stirrer and dropping funnel. The mixture was cooled to -5° in a Dry Ice-methanol-water slurry and about 600 ml. of a solution of chromium trioxide (200 g., 2.0 moles) and sulfuric acid (320 ml.) in water (900 ml.) was added dropwise at such a rate that the temperature did not rise above 0°. Ten minutes after complete addition of the oxidant, the reaction mixture gave a positive test with 0.4% diphenylamine sulfonate solution for excess oxidant. Chloroform (200 ml.) was then added and the mixture was stirred for 10 min. at 0°. The layers were separated and the aqueous layer was extracted twice with 200-ml. portions of 1:1-methylene chloride: chloroform. The combined organic layers were washed once with 100 ml. of water and dried over magnesium sulfate. Evaporation of the solvent at room temperature and reduced pressures afforded 37.88 g. (78.2%) of 4-cyclopenten-1, 3-dione, m.p. 32.0-33.5°, sufficient in purity for the subsequent steps.

3a, 4, 7, 7a-Tetrahydroindan-1, 3-dione (IIIa). - A solution of 75.0 g. (0.78 mole) of 4-cyclopenten-1, 3-dione, 90 ml. (58 g., 1.1 moles) of butadiene and 0.3 g. of 2, 5-di-*t*-butylhydroquinone in 220 ml. of benzene was allowed to stand in an autoclave at room temperature for 12 days. An additional 40 ml. (26 g., 0.48 mole) of butadiene was added and the mixture was allowed to stand for an additional 5 days. After the reaction mixture had been filtered to separate 94.4 g. (80.6%) of the crude product, m.p. 157.5-161°, concentration of the mother liquor followed by crystallization from ether afforded 6.02 g. (8% recovery) of the unchanged starting material, m.p. 33-34.5°. Recrystallization from a methanol-ethyl acetate mixture afforded the pure adduct IIIa as white prisms, m.p. 160-161.5°, lit.[4] m.p. 157.5-158.5°, with infrared absorption[10] at 1635 and 1585 cm.$^{-1}$ (enolic *β*-diketone) and an ultraviolet maximum[11] at 244.5 mμ(ϵ 15,400).

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[10] Determined as a suspension in a potassium bromide pellet.
[11] Determined as a solution in 95% ethanol.

Anal. Calcd. for $C_9H_{10}O_2$: C, 71.97; H, 6.71. Found: C, 72.01; H, 6.72.

A suspension of 25.7 g. (0.17 mole) of the enolic diketone IIIa in 70 ml. of methanol which had been saturated with hydrogen chloride was stirred at room temperature for 8 hr. The resulting solution was added, dropwise and with stirring, to an excess of cold (10°), aqueous potassium carbonate. After the resulting mixture had been extracted with ether, the ethereal solution was washed with water, dried and concentrated. Distillation of the residue afforded 23.31 g. (83%) of the enol ether IIIc, b.p.

91-96° (0.07 mm.), which solidified on standing, m.p. 40.3-41.7°. Recrystallization from ether afforded the pure enol ether as white prisms, m.p. 42.5-42.6°, with infrared absorption[12] at 1685 cm.$^{-1}$ (C=O) and 1595 cm.$^{-1}$ (C=C) and an ultraviolet maximum at 239 mμ (ε 15,700). Acidification of the aqueous potassium carbonate layer from this preparation followed by appropriate manipulations separated 1.16 g. (4.5%) of the starting material.

<u>Anal.</u> Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.11; H, 7.41.

Reaction of 2.00 g. (13 mmoles) of the enolic diketone IIIa with excess diazomethane in an ether-methanol mixture followed by concentration and distillation afforded 1.90 g. (87%) of the same enol ether IIIc, b.p. 105° (0.9 mm.), m.p. 37.5-39.0°, identified by comparison of the infrared spectra of the two samples.

<u>Piperylene (trans 1,3-pentadiene).</u> - 2-Penten-4-ol (n_D^{24} 1.4270, 102.3 g., 1.19 moles), prepared by the reaction of methylmagnesium bromide with crotonaldehyde, was combined with 200 g. of powdered, freshly fused potassium hydrogen sulfate. The mixture was heated in a bath kept at 130-170° while the diene and water distilled through an unheated column packed with chopped, perforated steel ribbon. The distillate was cooled in a Dry Ice-acetone bath to reduce evaporation loss. Redistillation of the products afforded 65.3 g. (80%) of piperylene, b.p. 39-41°, $n_D^{21.5}$ 1.4298.

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[12] Determined as a solution in chloroform.

This material had absorption in the infrared spectrum[13] at 1000, 950 and 900 cm.$^{-1}$ (C=C) and 1650 and 1605 cm.$^{-1}$ (conj. C=C). The ultraviolet spectrum[11] has a maximum at 223 mμ (ε 23,800). Vapor phase chromatography[14] indicated that the *trans* isomer (retention time, 8 min.) amounted to greater than 95% of the mixture, the *cis* isomer (retention time, 9 min.) being the only other component present. Reported for piperare n_D^{20} 1.4292-1.4306 and b.p. 41.5-41.9°.[15]

7-Methyl-3a,4,7,7a-tetrahydroindan-1,3-dione (IIIb). - A solution of 242 mg. (2.5 mmoles) of the enedione II, 430 mg. (6.3 mmoles) of *trans*-1,3-pentadiene and a few crystals of 2,5-di-t-butylhydroquinone in 1 ml. of benzene was allowed to stand at room temperature for 2 days. Filtration separated 368 mg. (89%) of the crude adduct, m.p. 145-146.5°. The pure enolic diketone IIIb crystallized from a methanol-ethyl acetate mixture as white microprisms, m.p. 149.5-150.5°, whose melting point was raised to 150.5-151° by sublimation under reduced pressure. The product has broad infrared absorption[10] at 1590 and 1630 (shoulder) cm.$^{-1}$ (enolic *β*-diketone) with an ultraviolet maximum at 245 mμ (ε 15,000).

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13) Determined as a solution in carbon tetrachloride.

14) A gas chromatography column packed with Dow Corning Silicone Fluid No. 710 on 60-80 mesh firebrick was employed for this analysis.

15) J. F. Busset, K. W. Greenlee, J. M. Derfer and C. E. Board, J. Am. Chem. Soc., *78*, 6076 (1958).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.91; H, 7.15.

cis-Hexahydroindan-1,3-dione (IV). - A solution of 1.28 g. (8.6 mmoles) of the enolic diketone IIIa in 25 ml. of methanol was hydrogenated at room temperature and atmospheric pressure over 130 mg. of a 30% palladium on carbon catalyst. After the absorption of 239 ml. (9.7 mmoles) of hydrogen, the reaction was stopped and the mixture was filtered and then concentrated. Crystallization of the residue from an ether-ethyl acetate mixture afforded 0.86 g. (67%) of the enolic diketone IV as white plates, m.p. 86.6-88°. The pure diketone IV, obtained after recrystallization, melted at 87.9-89.3°, lit.[4] m.p. 86-86.5°, exhibits infrared absorption[12] at 1725, 1635 and 1590 (broad) cm.$^{-1}$ (partially enolized *β*-diketone) with an ultraviolet maximum[11] at 243 mμ (ε 17,000).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.90; H, 8.10.

Preparation and Reactions of the Trienone VII. - A cold (0°) ethereal solution of 12.76 g. (0.78 mole) of the enol ether IIIc was added, dropwise and with stirring in a nitrogen atmosphere, to 100 ml. (0.107 mole) of a 1.07 *N* solution of vinylmagnesium chloride in tetrahydrofuran. After the addition was complete, the mixture was stirred at 0° for 2 hr. and then treated with saturated, aqueous ammonium chloride (adjusted to *p*H 7 by the addition of aqueous ammonia). After the organic layer had been separated and the aqueous phase had been extracted with ether, the combined organic solutions were dried and concentrated to leave 15.2 g. of the crude alcohol VI as a yellow oil with infrared absorption[13] at 1705 cm.$^{-1}$ (weak, C=O impurity), 1645 and 1620 cm.$^{-1}$ (C=C) and 925 cm.$^{-1}$ ($CH=CH_2$). To a cold (0°) solution of 14.4 g. of the crude alcohol VI and 10 mg. of 2,5-di-t-butylhydroquinone in 120 ml. of tetrahydrofuran was added 45 ml. of a cold (0°), very dilute aqueous solution of sulfuric acid (1 drop of sulfuric acid in 100 ml. of water). After the addition was complete, the mixture was stirred at 0° for 30 min. and then diluted with 500 ml. of ice water and extracted with petroleum ether. This extract was dried and concentrated under reduced pressure at room temperature. Distillation of the residue in a short-path still afforded 3.10 g. of the crude trienone VII as a yellow oil, b.p. 92-98° (0.2 mm.) with infrared absorption[13] at 1710 cm.$^{-1}$ (cyclopentenone C=O), 1640 and 1605 cm.$^{-1}$ (C=C) and 990 and 930 cm.$^{-1}$ ($CH=CH_2$), and an ultraviolet maximum[11] at 262 mμ (ε 14,400).

A solution of 415 mg. (2.6 mmoles) of the crude trienone VII, 28.5 mg. of 2,5-di-t-butylhydroquinone and 477 mg. (2.7 mmoles) of N-phenylmaleimide in 1.5 ml. of benzene was heated to 45-50° under a nitrogen atmosphere for 40 hr. Chromatography of the crude product on Merck acid-washed alumina separated 185 mg. (39%) of N-phenylmaleimide (eluted with benzene) and 414 mg. (48%) of the crude adduct VIII, m.p. 186-194° (eluted with methanol). Several recrystallizations from methanol and from ethyl acetate afforded the pure adduct VIII as white crystals, m.p. 203.5-205.5°, with infrared absorption[12] at 1780 (weak) and 1715 (broad, intense) cm.$^{-1}$ (C=O of 5-membered imide and cyclopentanone) and an ultraviolet maximum[11] at 221 mμ (ε 16,000).[16]

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[16] The absence of an ultraviolet maximum in the region 235-240 mμ indicates that the adduct has structure VII rather than the alternative structure in which the ketone and double bond functions are conjugated.

<u>Anal.</u> Calcd. for $C_{21}H_{19}NO_3$: C, 75.63; H, 5.74; N, 4.22. Found: C, 75.48; H, 5.95; N, 4.01.

A mixture of 1.134 g. (7.1 mmoles) of the crude trienone VII, 0.512 g. (7.1 mmoles) of acrylic acid and 2 mg. of 2,5-di-<u>t</u>-butylhydroquinone was heated in a sealed tube at 55° for five days. The partially polymeric reaction mixture was then extracted with methylene chloride and the organic layer was extracted with aqueous sodium bicarbonate solution. After this aqueous extract had been acidified and extracted with chloroform, the chloroform extract was dried and concentrated to leave a white solid. Recrystallization from ethyl acetate afforded 80.1 mg. (4.9%) of the adduct X as white prisms, m.p. 187-188°, with infrared absorption[12] at 1750 and 1700 cm.$^{-1}$ (C=O) and 1660, 1645 and 1630 cm.$^{-1}$ (C=C). The product has an ultraviolet maximum[11] at 236 mμ (ε 10,800). The NMR spectrum exhibits peaks[17] (60 mc.) at 4.2 τ (2H, broad, but not resolved, vinyl C-H), a series of broad, poorly resolved peaks in the region 6.7-8.0 τ corresponding to nine allylic and one carboxyl hydrogen atoms and a broad peak centered at 8.2 τ (4H, non-allylic methylene hydrogens).

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[17] Determined as a solution in perdeuterodimethylformamide.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.38; H, 6.94. Found: C, 72.36; H, 6.86.

The solution of neutral material from the above reaction was dried and condensed to an oil which afforded a solid upon trituration with ether. Recrystallization of this solid from an ether-ethyl acetate mixture afforded 0.138 g. (12%) of IX as white prisms, m.p. 130-133°. This material showed no depression of melting point with the sample described below and the two had identical infrared spectra.

The trienone VII (1.31 g., 8.2 mmoles) was combined with 12 mmoles of methacrolein at 55° for five days. Chromatography of this material through 40 g. of neutral alumina using benzene and benzene-ether mixtures as eluents gave 0.5425 g. (41%) of IX as an amorphous solid, m.p. 129-133°. An analytical sample had m.p. 135.8-136.7°, with infrared absorption[12] at 1690 cm.$^{-1}$ (cyclopentenone C=O), 1640 and 1615 cm.$^{-1}$ (C=C). The material had an ultraviolet maximum[11] at 235 mμ (ε 20,000), with NMR peaks[18] (60 mc.) at 4.2τ (5H, broad, but unresolved vinyl hydrogen atoms), a series of broad unresolved peaks in the region 6.4-8.0τ (15H, allylic hydrogen atoms divided 3:12; lower to higher field) and partially resolved peaks centered at 8.2τ (4H, non-allylic methylenes).

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.29; H, 7.60.

3a, 4, 7, 7a-Tetrahydroindenone XI. - To a cold (0°) solution of 68.0 g. (0.414 mole) of the enol ether IIIc in 200 ml. of ether was added, gradually with stirring, a solution of 6.5 g. (0.17 mole) of lithium aluminum hydride in 250 ml. of ether. The resulting mixture was refluxed, with stirring, for 1 hr. and then cooled and 25 ml. of water was added. The mixture was poured into excess cold, 10% aqueous sulfuric acid and the ether layer was separated. After the aqueous phase had been extracted with ether, the combined organic extracts were washed successively with aqueous sodium bicarbonate and water and then dried and concentrated. A short-path distillation of the residue separated 48.0 g. of colorless liquid containing[14] 75-80% of the desired product XI. Fractional distillation through a 40-cm. spinning-band column afforded 17.51 g. (32.4%) of fractions, b.p. 118-119° (20 mm.), n_D^{25} 1.5250-1.5256, containing[14] more than 95% of the desired ketone XI as well as 23.56 g. of intermediate fractions, b.p. 104-118° (20 mm.), n_D^{25} 1.5044-1.5243, containing mixtures of the desired ketone XI and lower-boiling impurities. The pure ketone XI has infrared absorption[13] at 1710 cm.$^{-1}$ (C=O) with ultraviolet maxima at 221 mμ (ϵ 8450) and 315 mμ (ϵ 40). The NMR spectrum[13] (60 mc.) of the material has two quadruplets centered at 2.52τ (1H, J 6 and 3 c.p.s., vinyl proton *beta* to C=O) and 3.91τ (1H, J 6 and 2 c.p.s., vinyl proton *alpha* to C=O), a partially resolved multiplet centered at 4.23τ (2H, vinyl protons of cyclohexene ring), a broad multiplet centered at 6.74τ (1H, tertiary proton *alpha* to C=O) and a complex multiplet in the region 7.4 to 8.0τ attributable to the remaining five allylic protons in the molecule.

Anal. Calcd. for $C_9H_{10}O$: C, 80.55; H, 7.51. Found: C, 80.47; H, 7.76.

A solution of 4.8 g. (0.028 mole) of the unsaturated ketone XI, 4.7 g. (0.028 mole) of dicyclopentadiene and 0.2 g. of 2,5-di-t-butylhydroquinone in 7 ml. of benzene was heated to 175° for 2 days in a sealed tube. Distillation of the reaction mixture in a short-path still separated 6.24 g. of volatile material, b.p. 90-140° (0.3 mm.). A solution of this material in an ether-petroleum ether mixture deposited 2.85 g. (60%) of the crude dienone XII, m.p. 61-74°. This product was sublimed under reduced pressure and then recrystallized from an ether-petroleum ether mixture to separate the pure dienone XII as white prisms, m.p. 76.5-77°, yield 1.68 g. (35%). The product has infrared absorption[13] at 1700 cm.$^{-1}$ (cyclopentenone C=O), 1675 and 1635 cm.$^{-1}$ (C=C) with ultraviolet maxima[11] at 220 mμ (ε 6,000) and 244 mμ (ε 6,400).[19] The NMR spectrum[13] (60 mc.) of the product has a partially resolved multiplet centered at 4.24τ attributable to two vinyl protons and a complex series of peaks in the region 7 to 8τ attributable to eight allylic protons.

Anal. Calcd. for $C_9H_{10}O$: C, 80.55; H, 7.51. Found: C, 80.38; H, 7.40.

The product XII formed a semicarbazone which crystallized from methanol as a white solid, m.p. 235° dec., yield 60%.

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.98. Found: C, 62.61; H, 6.83; N, 21.88.

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19) The appearance of the maximum at abnormally long wavelength is comparable to the spectra of 2,5-dihydroacetophenone and 6-methyl-2,5-dihydroacetophenone which both have maxima at 245 mμ (ε 5000), E. A. Braude, E. R. H. Jones, F. Sondheimer and J. B. Toogood, J. Chem. Soc., 607, (1949).

The gas chromatograph[14] of the mother liquors remaining after removal of the ketone XII indicated a complex mixture of products which was not further investigated.

A solution of the dienone XII (50 mg., 0.37 mmole) in 15 ml. of ether was hydrogenated at atmospheric pressure in the presence of 10 mg. of 5% palladium on charcoal catalyst. When hydrogen uptake had ceased (6.6 cc., theoretical 8.3 cc.) the catalyst was removed and the solution was concentrated. Vapor phase chromatography[14] indicated a complex product mixture with three components predominating. These components were isolated by vapor phase chromatography and were submitted for infrared analyses. The major component corresponding to 45% of the products had an infrared spectrum[13] identical with that of 4, 5, 6, 7-tetrahydro-1-indanone XIV. The other two components each corresponding to about 20% of the product mixture had infrared spectra[13] which compared very favorably with those of 1-hydrindanone and indane.

The dienone XI (3.46 g., 0.0258 mole), freshly prepared cyclopentadiene (1.70 g., 0.039 mole) and 3 ml. of benzene were heated at 170° for two days in a sealed tube. The mixture was then distilled, the product being collected in three fractions. The first two fractions (2.060 g.) b.p. 116° at 15 mm. to 82° at 0.15 mm., contained[14] a complex mixture of components of which the starting material was a predominate one; another major component had an infrared spectrum[13] similar to, but not identical with that of the dienone XII. The final fraction, 2.136 g., b.p. 82-110° at 0.15 mm., partially solidified and was recrystallized from an ether-petroleum ether mixture to afford 0.412 g. of a white solid, m.p. 102-105°. Further recrystallizations gave material, m.p. 107-107.5°, prisms, with infrared absorption[13] at 3075 and 1590 cm.$^{-1}$ (C=C-H) and 1710 cm.$^{-1}$ (C=O of cyclopentenone), and a maximum in the ultraviolet spectrum[11] at 225 mμ (O.D. = 1.44 for a 3.13 g./l. solution).

Anal. Calcd. for $C_{14}H_{16}O$ (for XV): C, 83.96; H, 8.05. Found: C, 84.27; H, 7.97.

Cyclopentan-1,3-dione (Va) and Its Enol Ether Vb. - Reduction of 4-cyclopenten-1,3-dione (2.00 g., 0.028 mole) with zinc in acetic acid as previously described[2a] afforded the saturated, enolic dione Va (1.75 g., 49%) as white prisms from a methanol-ethyl acetate mixture, m.p. 151-152° (lit.[2a] 149-150°), with an ultraviolet maximum[11] at 243 mμ (ε 17,500) and infrared absorption (Nujol mull) comparable to that reported[20] (only broad, general absorption with no distinguishing peaks).

Reaction of the diketone Va (0.924 g., 9.4 mmoles) with an excess of diazomethane in an ether-methanol mixture followed by concentration afforded an oil which on sublimation gave 0.8155 g. (77%) of white prisms, m.p. 49-50°. An analytical sample purified by recrystallization from an ether-cyclohexane mixture followed by sublimation had m.p. 51.3-52.1°, with infrared absorption[13] at 1705 (C=O), 1680 (C=C-OC) and 1600 cm.$^{-1}$ (C=C) and an ultraviolet maximum[10] at 237 mμ (ε 20,000). The NMR spectrum[13] (60 mc.) of this material has a finely resolved triplet at 4.75τ

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20) J. H. Boothe, R. G. Wilkinson, S. Kushner and J. H. Williams, J. Am. Chem. Soc., 75, 1732 (1953).

(1H, vinyl hydrogen J= 1.1 c.p.s.), a singlet at 6.16τ (3H, methoxyl hydrogens) and a well split, but complicated A_2B_2 pattern centered at 7.58τ (4H, methylene hydrogens).

Anal. Calcd. for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.02; H, 7.29.

Cyclopentenone.[21] In a vacuum distillation apparatus equipped with a Claisen distilling head was placed 50 g. (0.50 mole) of a mixture of cyclopentenediols and 1.2 g. of p-toluenesulfonic acid. The temperature of the heating bath was gradually increased from 130° to 180° as the ketone and water distilled with nitrogen ebullation under reduced pressure (10 mm.) into a Dry Ice-acetone cooled flask. Redistillation of the distillate afforded 22.56 g. of cyclopentenone, b.p. 151-153°, n_D^{18} 1.4817. The forerun was continuously extracted with methylene chloride and the organic layer was concentrated and distilled to afford 4.64 g. of additional cyclopentenone, b.p. 149-152°, n_D^{25} 1.4786, (lit.[21] b.p. 150-151°). Total yield amounted to 27.2 g. (66.4%). The cyclopentenone had a maximum in the ultraviolet spectrum at 218 mμ (ϵ 11,000) and infrared absorption[13] at 1710 (C=O) and 1590 cm.$^{-1}$ (C=C). Vapor phase chromatography[14] indicated that only one volatile component was present. The NMR spectrum[13] has a sharply resolved sextet (J= 5.7, 2.6 c.p.s.) centered at 2.32τ (1H, β-vinyl hydrogen), another well-resolved sextet (J= 5.7, 2.1 c.p.s.) at 3.92 (1H, α-vinyl hydrogen, plus well-resolved splitting in the regions 7.2-7.5τ and 7.7-7.9τ (4H, methylene hydrogens).

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21) This is a modification of the procedure described by C. H. DePuy and K. L. Eilers, J. Org. Chem., **24**, 1380 (1958).

Attempted Reaction of Methyl *trans*-2, 4-Pentadienoate (XVIb) with Cyclopentenone. - A solution of 22.4 g. (0.27 mole) of cyclopentenone, 18.75 g. (0.167 mole) of the diene XVIb and 4.7 g. of 2, 5-di-*t*-butylhydroquinone in 50 ml. of benzene was heated at 115-125° in an autoclave for 13 days. The resulting mixture was chromatographed on 370 g. of neutral alumina. The non-polymeric product, elute with benzene, was distilled in a short-path still to separate 5.994 g. of yellow liquid, b.p. 110-112° (0.25 mm.), containing[14] one major component. Fractional distillation through a Holtzmann column separated 2.0195 g. of colorless liquid, b.p. 104° (0.04 mm.), n_D^{25} 1.4942, containing[14] only the previously mentioned major component, namely the diester XX. This material had infrared absorption[13] at 1740 (shoulder) and 1730 cm.$^{-1}$ (unconj. and conj. ester C=O) and 1655 cm.$^{-1}$ (C=C) with ultraviolet maxima[11] at 207 mμ (ϵ 11,800) and 302 mμ (ϵ 83). The NMR spectrum[13] (60 mc.) exhibits a quadruplet centered at 3.11τ (1H, J 16 and 8, vinyl proton beta to ester function), a multiplet at approximately 4.2τ (3H, vinyl proton alpha to ester functions and two vinyl protons of the cyclohexene moiety), a singlet at 6.33τ (6H, $COOCH_3$) and broad unresolved absorption in the region 6.7-8.5τ.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.55; H, 7.23.

Methyl 2, 4-pentadienoate XVIb (81 mg., 0.72 mmole) was dissolved in five times its volume of benzene and the mixture was saturated with 2, 5-di-*t*-butylhydroquinone. This mixture was sealed in an ampule and was heated at 120° for twelve days. The mixture was concentrated to a heavy oil which was distilled (b. p. 110° at 0. 06 mm.) to give 37 mg. of a liquid which had infrared absorption[13] identical to that of the material characterized above.

Diels-Alder Reactions with Pentadienoic Acid (XVIa) and Its Ester (XVIb). - A mixture of 5. 16 g. (0. 046 mole) of the ester XVIb, 5. 23 g. (0. 054 mole) of the enedione II and 380 mg. of 2, 5-di-*t*-butylhydroquinone was allowed to stand at room temperature under nitrogen for 23 days. A solution of the resulting mixture in a methanol-ethyl acetate mixture deposited 4. 55 g. of the adduct XIXb, m. p. 181-182. 5°. Extraction of the mother liquor with aqueous potassium carbonate followed by acidification of the aqueous extract and appropriate manipulations afforded an additional 0. 491 g. (total yield 5. 04 g. or 53%) of the adduct. Recrystallization gave the pure enolic diketo ester XIXb as white prisms, m. p. 182. 9-183. 9°, with infrared absorption[10] at 1735 cm. $^{-1}$ (ester C=O) and 1630 (shoulder) and 1580 cm. $^{-1}$ (enolic *β*-diketone) with an ultraviolet maximum at 244 mμ (ϵ 13, 800).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63. 45; H, 5. 84. Found: C, 63. 17; H, 5. 75.

After a solution of 0. 75 g. (7. 7 mmoles) of the acid XVIa, 0. 75 g. (7. 8 mmoles) of the enedione II and 3 mg. of 2, 5-di-*t*-butylhydroquinone in 3 ml. of benzene had been allowed to stand at room temperature for ten days, the solid which separated was filtered and washed with ether to leave 175 mg. (11%) of the crude adduct, m. p. 184. 7-185° dec. Recrystallization from a methanol-ethyl acetate mixture gave the pure adduct

XIXa as white amorphous solid, m.p. 191.3° dec., with infrared absorption[10] at 1695 cm.$^{-1}$ (carboxyl C=O) and 1655 and 1595 cm.$^{-1}$ (enolic β-diketone) and an ultraviolet maximum at 245 mμ (ϵ 15,200).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.89; H, 5.38.

A solution of 100 mg. (5.8 mmoles) of N-phenylmaleimide and 65 mg. (5.8 mmoles) of the ester XVIb in 0.5 ml. of benzene, saturated with 2,5-di-t-butylhydroquinone, was allowed to stand to room temperature for 18 days and then concentrated under reduced pressure. Trituration of the residue with ether left 147 mg. (87%) of the crude adduct, m.p. 120-123°. Recrystallization from an ether-ethyl acetate mixture followed by sublimation under reduced pressure afforded the pure adduct XVIIIb as white prisms, m.p. 123-124°. The product has infrared absorption[12] at 1710 (broad) cm.$^{-1}$ with shoulders at 1740 and 1780 cm.$^{-1}$ (C=O of ester and 5-membered imide) with end absorption in the ultraviolet[11] and a point of inflection at 215 mμ (ϵ 2,600).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.35; H, 5.33. Found: C, 67.23; H, 5.27.

After a solution of 165 mg. (9.5 mmoles) of N-phenylmaleimide and 118 mg. (8.3 mmoles) of the acid XVIa in 1 ml. of benzene had been allowed to stand at room temperature for 40 hr., the solid which separated was recrystallized from methanol to give 165 mg. (50%) of the adduct XVIIIa as white prisms, m.p. 225-226.5° dec. Recrystallization raised the decomposition point to 230-231°. The material has infrared absorption[10] at

1775 and 1730 cm.$^{-1}$ (C=O of imide in a 5-membered ring) and 1690 cm.$^{-1}$ (carboxyl C=O) with end absorption in the ultraviolet[11] at 214 mμ, (ϵ 11, 000).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.33; H, 4.66; N, 5.22.

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1) For a recent review see J. F. Grove, Quart. Revs., 15, 56 (1961).

2) (a) C. H. DePuy and E. F. Zaweski, J. Am. Chem. Soc., 81, 4920 (1959).
(b) C. H. DePuy and C. E. Lyons, J. Am. Chem. Soc., 82, 631 (1960).

3) H. O. House, G. H. Rasmusson, C. H. DePuy and E. F. Zaweski, Org. Syntheses, in press.

4) Since completion of this work the synthesis of this material has been reported by V. F. Kucherov and L. I. Ivanova, Doklady Akad. Nauk., S.S.S.R., 131, 1077 (1960); C.A., 54, 21021b (1960).

5) For a detailed account of these data see the experimental section.

6) J. G. Martin and R. K. Hill, Chem. Revs., 61, 537 (1961).

7) (a) I. N. Nazarov, A. I. Kuznetsova and N. V. Kuznetsov, J. Gen. Chem., U.S.S.R., 25, 75 (1955).
(b) I. N. Nazarov, Y. Titov and A. I. Kuznetsova, Acad. Sci. U.S.S.R., Chem. Sci. Bull., 1224 (1959).
(c) K. Alder, J. Hayden, K. Heimbach and K. Newfang, Ann., 586, 110 (1954).
(d) K. Alder, et. al., Ann., 564, 79 (1949).

8) The synthesis of this material is described in the Appendix; see also H. O. House and G. H. Rasmusson, J. Org. Chem., 26, 4278 (1961).

9) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird, model B, or a Perkin-Elmer, model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 11MS. The microanalyses were performed by Dr. S. M. Nagy
an and his associates and by the Scandinavian Microanalytical Laboratory. Unless otherwise stated magnesium sulfate was employed as a drying agent. The NMR spectra were determined with a Varian, model A-60, NMR spectrometer.

10) Determined as a suspension in a potassium bromide pellet.

11) Determined as a solution in 95% ethanol.

12) Determined as a solution in chloroform.

13) Determined as a solution in carbon tetrachloride.

14) A gas chromatography column packed with Dow Corning Silicone Fluid No. 710 on 60-80 mesh firebrick was employed for this analysis.

15) J. F. Busset, K. W. Greenlee, J. M. Derfer and C. E. Board, J. Am. Chem. Soc., 78, 6076 (1958).

16) The absence of an ultraviolet maximum in the region 235-240 mμ indicates that the adduct has structure VIII rather than the alternative structure in which the ketone and double bond functions are conjugated.

17) Determined as a solution in perdeuterodimethylformamide.

18) Determined as a solution in deuterochloroform.

19) The appearance of the maximum at abnormally long wavelength is comparable to the spectra of 2, 5-dihydroacetophenone and 6-methyl-2, 5-dihydroacetophenone which both have maxima at 245 mμ (ε 5000), E. A. Braude, E. R. H. Jones, F. Sondheimer and J. B. Toogood, J. Chem. Soc., 607, (1949).

20) J. H. Boothe, R. G. Wilkinson, S. Kushner and J. H. Williams, J. Am. Chem. Soc., 75, 1732 (1953).

21) This is a modification of the procedure described by C. H. DePuy and K. L. Eilers, J. Org. Chem., 24, 1380 (1958).

SECTION II

CHEMISTRY OF POLYHYDROINDANONES

PART II

STABILITY RELATIONSHIPS

As an extention of studies directed toward the synthesis of polyhydroindanones by Diels-Alder reactions[1] we were led to explore the reaction of dienes with cyclopentenone (I). Very little research has been done in this area, primarily because cyclopentenone has not been a practical intermediate. The recently reported preparation of cyclopentenone from a readily available precursor[2] made it appear as an attractive synthetic intermediate for work in these laboratories directed toward the synthesis of the gibberellins.

The reaction between cyclopentenone and butadiene has been reported.[3] In this report the Diels-Alder product could not be isolated as such and was characterized as a derivative. Upon reinvestigation of this reaction we found that the adduct could be isolated in moderate yield (20-30%). It was somewhat surprising to find that there were actually two products formed in nearly equal amounts under the conditions employed for the reaction (110° for 12 days). That these were actually the isomeric tetrahydroindanones II and III was obvious from the fact that they both gave

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1) See Section II, Part I of this thesis.

2) C. H. DePuy and K. L. Eilers, J. Org. Chem., 24, 1380 (1958).

3) E. Dane and K. Eder, Ann., 539, 207 (1939).

the same dinitrophenylhydrazone and when each was treated with base they gave the same mixture of isomers. Pure samples of II and III could be obtained by fractional distillation. Reduction of each of these isomers gave the corresponding *cis* and *trans* hydrindanones, V and VI. The higher boiling isomer was shown to have the *cis* ring juncture (II) by identifying its reduction product with authentic *cis* 1-hydrindanone prepared by reduction product with authentic *cis* 1-hydrindanone prepared by reduction of the ketone IV.[4] By employing lower reaction temperatures (100°) over a shorter period of time we found that the kinetically favored[5] product II predominated in the reaction mixture. This further verified the stereochemistry assigned to II and III.

The same mixture of ketones (II and III) could be obtained by the stannic chloride[6] catalyzed reaction of I with butadiene. However, this method was generally inferior to the thermal reaction in yield, workup and product purity. In the thermal reaction much cyclopentenone remained unchanged but its recovery was complicated by the presence of another component of similar boiling point, probably a trimer of butadiene. Thus, one might expect higher yields than those obtained if a larger excess of buta-

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4) D. W. Mathieson, J. Chem. Soc., 3248 (1953).

5) For a review of the stereochemistry of the Diels-Alder reaction see J. G. Martin and R. K. Hill, Chem. Revs., *61*, 537 (1961).

6) R. Robinson and G. I. Fray, Brit. Pat. 835,840, May 25, 1960.

diene were employed.

With the more reactive diene trans piperylene (trans 1,3-pentadiene, VII) the Diels-Alder reaction with cyclopentenone proceeded to give adducts in greater than 70% yield. When the reaction was run at 155° for two days a mixture of products was obtained. The predominant product (70% of the mixture) was the trans 7-methyl compound IX. That it was the 7-methyl compound was shown when this material was dehydrogenated to the corresponding indanone XIII. Evidence showing that this material was the trans isomer came when the corresponding reaction was run at a lower temperature (85°, one week). In this case the milder reaction conditions afforded predominantly the kinetically favored[5] cis epimer VIII (ca. 65% of the products). The cis isomer was isomerized completely to the trans isomer by treatment with base or by continued heating of the reaction mixture.

The stereochemistry assigned to compounds VIII, IX, XI and XII at atoms C-3a and C-7 is based on the observed[5] cis, endo addition of the dienes to dienophiles. Thus, the addition of trans dienes such as VII gives a system in which all groups on the six-membered ring are cis to one another (e.g. VIII).

The 4-methyl isomer(s) X was also produced in this reaction as evidenced by the presence of 4-methylindanone XIV as one of the dehydrogenation products. Cyclization[7] of the acid XV, prepared by malonate con-

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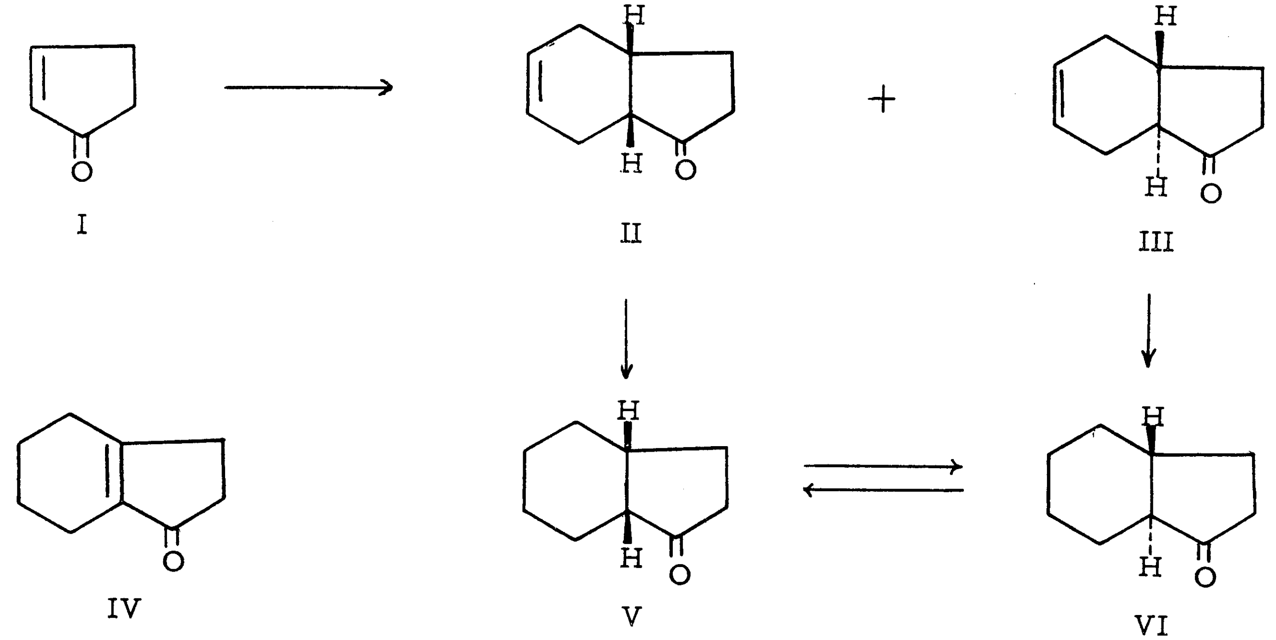
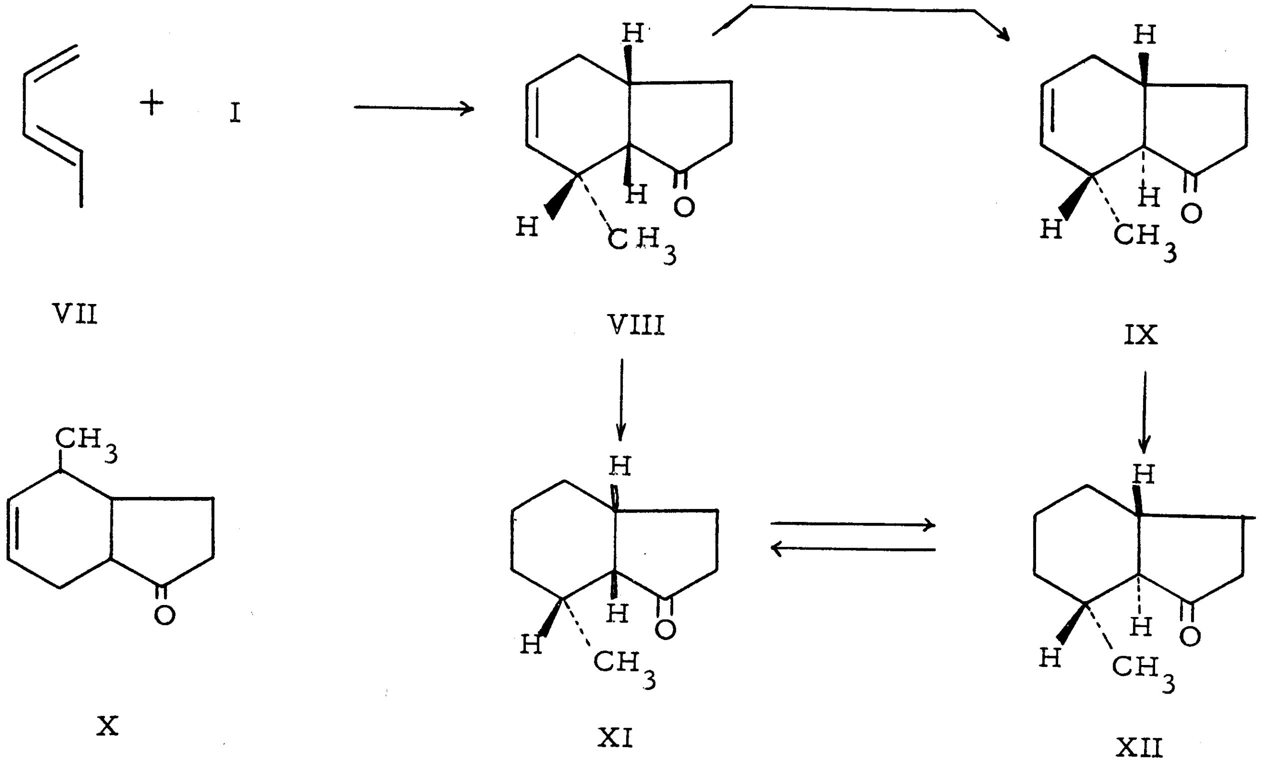
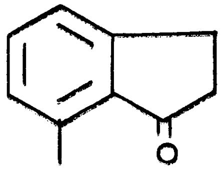
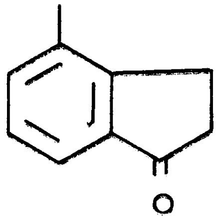
[7] S. Dev, J. Indian Chem. Soc., 32, 403 (1955).


I
II
III
IV
V
VI

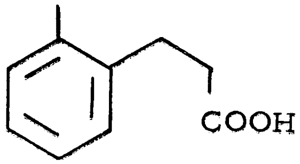

VII
VIII
IX
X
XI
XII



XIII

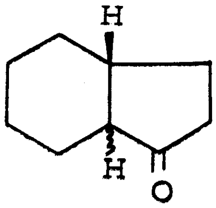
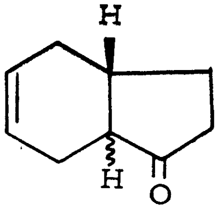
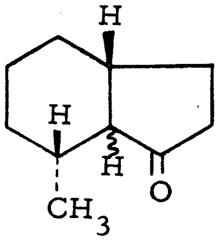
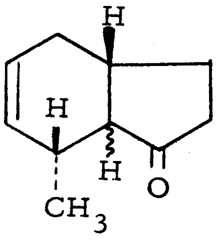


XIV



XV

TABLE

STRUCTURE	%TRANS ISOMER AT EQUIL.
	25
	47.5
	75
	99

densation with α-bromo-o-xylene followed by decarboxylation, afforded an authentic sample of XIV.

The 7-methylhydrindanones XI and XII could be obtained as the predominant products from catalytic reduction of the corresponding Diels-Alder adducts VIII and IX.

The stability of hydrindanone systems has been of much interest,[8] particularly in the field of natural products where this system is frequently encountered. It was of interest then to determine the position of equilibrium in the simple polyhydroindanone systems encountered in this work as they might provide information which studies in the more complex systems could use to advantage.

The position of equilibrium of the compounds studied is shown in the table. The positions of equilibrium were determined by vapor phase chromatography of samples equilibrated at 100° in triethylamine.

Little may be said concerning the stability of 1-hydrindanone as it lies in the direction predicted,[9] although not as far in favor of the cis isomer as one might expect.[8] It becomes readily apparent that the presence of the methyl group at position 7 and cis to the C_3-C_{3a} bond causes the stability of the hydrindanone system to shift in favor of the trans epimer.

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8) For a review see G. Quinkert, Experientia, 13, 381 (1957) and the historical review in this section of the thesis.

9) W. Huckel, M. Sachs, Y. Yantschulewitsch and F. Nerdel, Ann., 518, 135 (1935).

This, then, is another of the rare instances where a trans hydrindanone is the more stable.[10] The examples cited here offer another[11] opportunity to study conformational effects in determining stabilities of these systems.

An observation of the conformations XIa and XIb shows that the methyl hydrindanone does not have the freedom to share two conformations of nearly equal energy by ring flip such as can be found in the case of the parent cis hydrindanone. The conformation XIb has serious 1,3-diaxial interactions and probably restricts this compound to existing primarily in the conformation XIa. This should greatly lower the entropy of this system relative to that of the parent compound and, thus, be an added factor of instability.[12] Probably more important is the tendency of the five-membered ring in the cis compound XIa to flatten the six-membered ring[13] causing the methyl and carbonyl functions to approach the energetic eclipsed conformation. In the trans compound XIIa the effect is reversed in that the increased buckling of the six-membered ring causes these functions to

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10) D. H. R. Barton and G. F. Laws, J. Chem. Soc., 52 (1954).

11) J. F. Biellmann, D. Francetic and G. Ourisson, Tetrahedron Letters, no. 18, 4 (1960).

12) For a similar discussion see N. L. Allinger, J. Org. Chem., 21, 915 (1956).

13) For a discussion of these effects see W. G. Dauben and K. S. Pitzer in M. S. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 37.

adopt more favorable positions relative to one another.

The introduction of a 5, 6-double bond into these molecules also gave interesting results, for in the octalin series the introduction of a double bond in an analogous position afforded a less stable *trans* compound and, thus, tended to favor the *cis* ring fusion.[14] The reverse effect found in the series studied here is probably the result of the preferred conformations of these materials. It is felt that the *cis* tetrahydroindanones exist in a boat conformation to avoid serious bond angle deformations.[15] This sets up another energetic situation, however, by eclipsing the C_7-C_{7a} and C_{7a}-C_1 bonds with the C_{3a}-C_4 and C_3-C_{3a} bonds, respectively. By examination of molecular models it can be seen that the *trans* isomers in this series have little to gain by being in a boat conformation and consequently should exist in the *quasi* chair form in which adjacent bond interactions are reduced.

The combined effects of a 7-methyl substituent and 5, 6-double bond completely reverse the usual order of stability found in the polyhydroindanones such that an equilibrium mixture contains only the *trans* isomer. It is easily seen by looking at models of the *cis* 7-methyl compound VIII that it is energetically less favorable than the corresponding *trans* epimer IXa.

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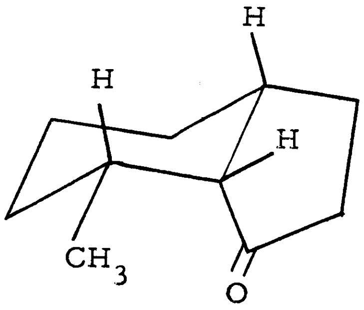
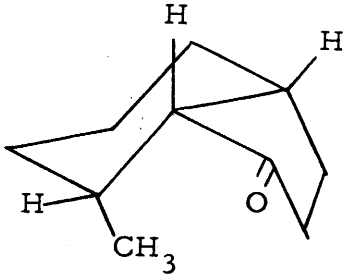
[14] For references and discussion see S. K. Balasubramanian, Tetrahedron, *12*, 196 (1961).

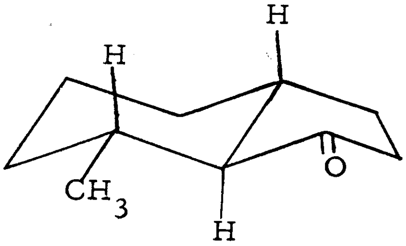
[15] For evidence of a similar system believed to contain the boat conformation see A. P. Gray, D. E. Heitmeier and H. Draus, J. Am. Chem. Soc., *84*, 89 (1962).



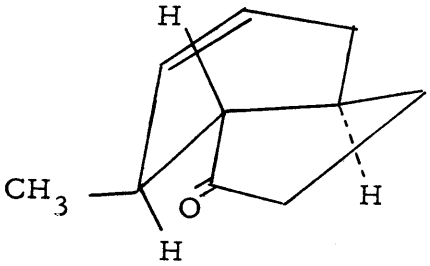
XIa



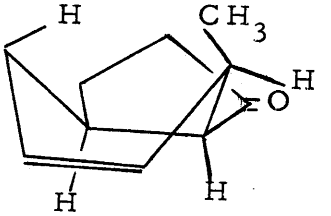
XIb



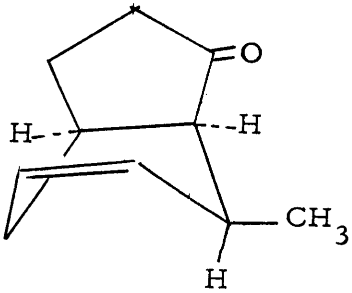
XIIa



IXa



VIIIa

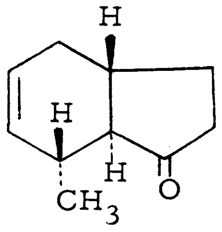


VIIIb

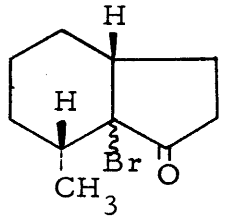
In the exo, boat conformation VIIIa has serious 1, 4-interaction between the methyl group and the axial hydrogen at carbon atom 4. In the endo, boat conformation VIIIb this effect is minimized, but the bonds between the methyl group and the carbonyl group are nearly eclipsed, again increasing the energy of the system.

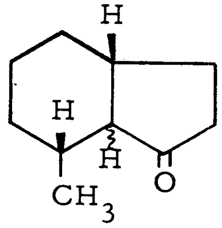
The 7-methyl compound IX appeared as a possible precursor to the tetrahydroindanone XVII desired as an intermediate in the synthesis of the carboxy-methylhydrindanone XVIII. Acid catalyzed migration of the double bond in IX afforded only material with an endocyclic double bond (XVI). When the hydrindanone derivative XII was halogenated, an unstable bromide was obtained which on loss of hydrogen bromide by various methods (lithium chloride, dimethylformamide; collidine; distillation, or pyridine) gave XVI as the predominant product with only a small amount of the desired ketone XVII. The enol acetate of IX was prepared in the hope that under the conditions of the reaction the 5, 6-double bond might move into conjugation to give compound XX. This reaction proceeded to give only the enol acetate XIX, and only the starting ketone could be obtained on hydrolysis.

The results cited above indicate that the endocyclic isomer XVI is apprecialy more stable than the exocyclic material XVII. The isomer XVII may be destabilized because of an eclipsing interaction between the methyl group and the carbonyl function which interferes with the planarity of the α, β-unsaturated system. In XVI this kind of destabilization is not effective because in this material the carbon to which the methyl group is attached is tetravalent and consequently the methyl group is out of the plane of the α, β-unsaturated system.

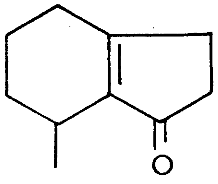


IX

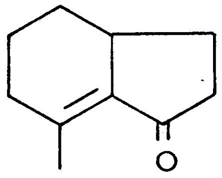




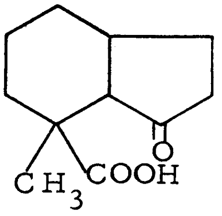
XII



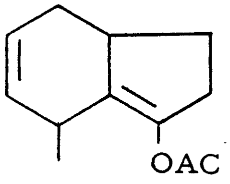
XVI



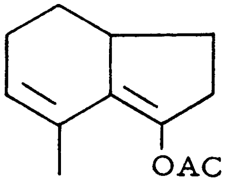
XVII



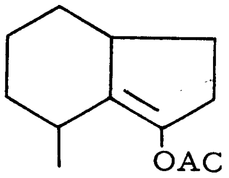
XVIII



XIX



XX



XXI

EXPERIMENTAL[16]

<u>Addition of butadiene to cyclopentenone.</u> - A solution of cyclopentenone[1] (85 g., 1.04 moles), butadiene (200 g., 3.7 moles) and 2,5-di-<u>t</u>-butylhydroquinone (10 g.) in 250 ml. of benzene were heated at 110° for twelve days in an autoclave. The mixture was then concentrated under reduced pressure at room temperature and the residue distilled under reduced pressure through a short-path still to give 128 g. of yellow liquid, b.p. 36-100° at 8 mm. Vapor phase chromatography[17] indicated that in addition to low boiling components, a mixture of 40% of the <u>trans</u> isomer III (first eluted) and 60% of the <u>cis</u> isomer II was obtained. The material was then fractionated on a 70-cm. spinning band column. A forerun (75.5 g.) distilled at 50-85° at 7 mm. and contained[17] two components in about equal amounts. One component was identified[17] as cyclopentenone. The remaining

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[16] All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird, model B, or a Perkin-Elmer, model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory. Unless otherwise stated magnesium sulfate was employed as a drying agent. The NMR spectra were determined with a Varian, model A-60, NMR spectrometer.

[17] A gas chromatography column packed with Dow Corning Silicone Fluid No. 710 on 60-80 mesh firebrick was employed for this analysis.

material distilled primarily in the range 91° at 7 mm. to 92° at 5 mm. to give 41.7 g. (29%) of the adducts II and III. The cis isomer II was obtained pure[17] in several fractions (5.1259 g.), b.p. 92° at 5 mm., n_D^{25} 1.5038. An analytical sample had infrared absorption[18] at 1735 (C=O) and 1655 cm.$^{-1}$ (C=C in cis fused ring) and only weak end absorption in the ultraviolet spectrum[19] (ϵ 400 at 210 mμ) as well as a maximum at 284 mμ (ϵ 26). The NMR spectrum[18] of this material shows a sharp slightly resolved peak at 4.4 τ (2H, vinyl hydrogen atoms) and broad, partially resolved absorption in the region 7.4-8.6 τ (10H, remaining methylene and methine hydrogen atoms).

Anal. Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88; M.W., 136. Found: C, 79.13; H, 8.86; M.W., 136 (mass spectrum).

The trans epimer III was obtained by refractionation on a 70-cm. spinning band column of 12.05 g. of the lower boiling fractions from the above mentioned fractional distillation. The pure material,[17] b.p. 99° at 12 mm., had n_D^{25} 1.4942 and infrared absorption[18] at 1740 (C=O) and 1635 cm.$^{-1}$ (C=C in trans fused ring). The ultraviolet spectrum[19] shows only weak end absorption (ϵ 294 at 210 mμ) and a maximum at 288 mμ (ϵ 34). The NMR spectrum[18] shows a sharp, partially resolved peak at 4.45 τ (2H, vinyl hydrogen atoms) and broad, partially resolved absorption at 7.4-8.7 τ (10H, remaining hydrogen atoms).

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18) Determined as a solution in carbon tetrachloride.

19) Determined as a solution in 95% ethanol.

Anal. Calcd. for $C_9H_{12}O$: C, 79.38; H, 8.87; M.W., 136. Found: C, 79.15; H, 8.89; M.W., 136 (mass spectrum).

Reaction of either the cis- (II) or trans (III) isomer with ethanolic 2,4-dinitrophenylhydrazine containing a few drops of hydrochloric acid produced the same 2,4-dinitrophenylhydrazone (as shown by mixed melting point and comparison of ultraviolet and infrared spectra), as orange microplates from an ethanol-ethyl acetate mixture, m.p. 201-201.5° dec. The yield was 46.5% from the cis isomer II and 42.5% from the trans isomer III. The material had an ultraviolet maximum[19] at 364 mμ (ϵ 2,800) and infrared absorption[20] at 1637 (shoulder, C=C in trans fused ring?), 1615 and 1590 cm.$^{-1}$ (aromatic).

Anal. Calcd. for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 57.07; H, 5.15; N, 17.52.

When a solution of butadiene (10 g., 0.185 mole), cyclopentenone (5.0 g., 0.061 mole) and 0.4 g. of 2,5-di-t-butylhydroquinone in 10 ml. of benzene were heated at 100° for four days and the product (0.984 g., 12%, b.p. 81-88° at 10 mm.) isolated, vapor phase analysis[17] indicated the cis epimer II predominated to the extent of 3:1 over the trans epimer.

Stannic chloride catalyzed addition of butadiene to cyclopentenone. To a solution of anhydrous stannic chloride (7.5 ml.) in 50 ml. of benzene was added cyclopentenone (6.00 g., 0.073 mole). The solution turned red and then 12 ml. of butadiene was distilled slowly into the stirred, cool

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20) Determined as a suspension in potassium bromide.

(0°) mixture. After complete addition the mixture was stirred at room temperature for 4 hr. Additional butadiene (6 ml.) was added and the mixture was stirred at room temperature overnight. Water was added to the mixture and the phases were well mixed. The organic phase was passed through potassium carbonate and dried. Distillation (13 mm.) afforded fractions of 0.6564 g., b.p. 59-79°, mainly cyclopentenone; 0.9474 g., b.p. 79-98°, mainly an equal mixture of II and III; and 0.7895 g., b.p. 98° up, a complex mixture of components.[17]

<u>β-Carbethoxy-β-(1-cyclohexenyl) propionic acid.</u> - This material was prepared by the method of Johnson, et. al.[21] The reaction of cyclohexanone (19.6 g., 0.20 mole) and diethyl succinate (52 g., 0.28 mole) in the presence of potassium *t*-butoxide (0.21 mole) afforded after the appropriate manipulations the desired Stobbe condensation product, 28.88 g. (64%), b.p. 148-153° at 0.47 mm., n_D^{25} 1.4921 (reported[21] n_D^{25} 1.4830, b.p. 150-155° at 0.5 mm.).

<u>4, 5, 6, 7-Tetrahydroindanone (IV).</u> - This material was prepared by the method of Mathieson.[4] Treatment of the Stobbe condensation product (28.5 g., 0.126 mole) obtained above with zinc chloride (5 g., 0.37 mole) in acetic acid-acetic anhydride afforded, after ring closure and decarbethoxylation, the pure[17] tetrahydroindanone IV (2.63 g., 15.5%), b.p. 121-125° at 15 mm., n_D^{27} 1.5200 (lit.[4] n_D^{18} 1.5260, b.p. 83.5-85° at 2 mm.). The material had infrared absorption[18] at 1698 (C=O of cyclopentenone) and

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[21] W. S. Johnson, C. E. Davis, R. H. Hunt and G. Stork, J. Am. Chem. Soc., <u>70</u>, 3021 (1948).

1645 cm.$^{-1}$ (C=C) with an ultraviolet maximum at 237 mμ (ϵ 1.35 x 10^4). The NMR spectrum[18] has broad partially resolved absorption in the region 7.4-8.1 τ (8H, hydrogen atoms allylic to double bond and alpha to carbonyl) and in the region 8.1-8.6 τ (4H, non-allylic methylene hydrogen atoms).

This material (IV) (1.882 g., 13.8 mmoles) was hydrogenated in the presence of 0.401 g. of palladium on charcoal catalyst at atmospheric pressure and room temperature in 35 ml. of methanol. The uptake of hydrogen amounted to 330 cc. (theor. 310 cc.). Removal of catalyst and solvent followed by distillation gave 1.6305 g. of cis hydrindanone V, b.p. 98° at 16 mm.; n_D^{27} 1.4805 (lit.[4] b.p. 72-73° at 6 mm., n_D^{25} 1.4813). The ketone has infrared absorption[18] at 1740 cm.$^{-1}$ and is identical with the spectrum of a sample prepared from the ketone II as described below.

cis Hydrindanone (V). - A solution of 400 mg. (2.95 mmoles) of the cis ketone II in 15 ml. of ether was hydrogenated over 40 mg. of a 30% palladium on carbon catalyst at room temperature and atmospheric pressure. After the absorption of hydrogen (59 cc., 0.91 equiv.) ceased the mixture was filtered and concentrated to leave 293 mg. (73%) of colorless liquid containing[17] 80% of the cis isomer V and 20% of the unsaturated ketone IV (identified by comparison of the infrared spectrum of a collected sample with that of the previously described material). The cis isomer V collected by vapor phase chromatography contained less than 11% of the trans isomer VI and had infrared absorption[18] at 1740 cm.$^{-1}$ (cyclopentanone C=O), ultraviolet maxima[19] at 288 mμ (ϵ 22) and at 237 mμ (ϵ 71, probably due to the presence of a trace of the unsaturated ketone IV), broad NMR absorption[18] in the region 7.5-9.2τ and a molecular weight (mass spectrum) of 138.

trans Hydrindanone (VI). - A solution of 1.30 g. (9.56 mmoles) of the trans ketone III in 25 ml. of ether was hydrogenated over 150 mg. of a 30% palladium on carbon catalyst at room temperature and atmospheric pressure. After hydrogen uptake ceased (260 cc., 1.2 equiv.) the mixture was filtered, concentrated and distilled to separate 0.7893 g. (64%) of the trans hydrindanone VI, b.p. 81.5-86.5° at 10 mm., n_D^{27} 1.4764, containing[17] less than 9% of the cis isomer V. The product had infrared absorption[18] at 1740 cm.$^{-1}$ (cyclopentanone C=O), ultraviolet maxima[19] at 288 mμ (ϵ 29) and 237 mμ (ϵ 37, this latter absorption is probably due to contamination with a small amount of the unsaturated ketone IV) and broad NMR absorption[18] in the region 7.5-9.2 τ.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21; M.W., 138. Found: C, 78.30; H, 10.33; M.W., 138 (mass spectrum).

Addition of piperylene to cyclopentenone. A. At high temperature. A mixture of cyclopentenone (16.02 g., 0.195 mole), piperylene[1] (30 g., 0.44 mole), 2,5-di-*t*-butylhydroquinone (2.04 g.) and 30 ml. of benzene were heated at 155° for 55 hr. The mixture was concentrated and distilled to give 31.59 g. of product, b.p. 70-110° at 11 mm. A redistillation separated 20.63 g. (71%) of the adducts, b.p. 95-104° at 13 mm. This mixture contained one main component (70% of the total) along with several minor products. The major component was greatly enriched by fractional distillation which gave fractions containing greater than 95% of the lower boiling *trans* ketone IX, b.p. 97-98° at 13 mm., n_D^{25} 1.4872. A *dinitrophenylhydrazone of IX* obtained (65%, yield) as a red microcrystalline solid after recrystallization from an ethanol-ethyl acetate mixture had m.p. 231-231.5° and infrared absorption[20] at 1635 (C=C), 1620 and 1590 cm.$^{-1}$. The ultraviolet maximum[19] of this material was at 364 mμ (ϵ 2.34×10^4).

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.29; H, 5.42; N, 16.81.

A pure sample of the *ketone IX* was obtained by vapor phase chromatography.[17] This sample had infrared absorption[18] at 1740 (cyclopentanone C=O) and 1635 cm.$^{-1}$ (double bond in *trans* fused ring) with only weak end absorption (ϵ 404 at 210 mμ) in the ultraviolet spectrum. The NMR spectrum[18] has a series of partially split peaks centered at 4.5τ (2H, vinyl hydrogen atoms) and broad unresolved abosrption between 7.4 and 8.9τ with the split methyl absorption (J= 6.8) centered at 8.83τ (12H, non-vinyl hydrogen atoms).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39; M.W., 150. Found: C, 80.15; H, 9.63; M.W., 150 (mass spectrum).

The ketone IX (0.636 g., 0.042 mole) was dehydrogenated by refluxing a *p*-cymene solution (6 ml.) under nitrogen in the presence of 125 mg. of a 30% palladium on charcoal catalyst for 17 hr. The product, eluted with benzene through neutral alumina, amounted to 0.249 g. (40.5%) of a crystalline solid, m.p. 40-50°. Recrystallization from petroleum ether afforded 130 mg. (21%) of the indanone XIII as pale yellow needles, m.p. 52.0-53.3°. An analytical sample prepared by sublimation had m.p. 54.7-

55.2°, infrared absorption[18] at 1710 (cyclopentenone carbonyl), 1600 (aromatic), 1375 and 1445 cm.$^{-1}$ (C-methyl) and ultraviolet maxima[19] at 249 mμ (ϵ 13,600) and 297 mμ (ϵ 2500). The NMR spectrum[22] shows five partially split peaks in the region 2.4-3.1τ (3H, aromatic hydrogen atoms), three partially resolved peaks in the region 6.8-7.1τ (2H, methylene hydrogen atoms *alpha* to carbonyl) and highly split absorption between 7.3 and 7.6τ including a singlet methyl peak at 7.39τ (5H, remaining hydrogen atoms).

Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 82.20; H, 6.83.

A *dinitrophenylhydrazone* separated (83% yield) from a methanol-ethyl acetate mixture as red prisms and had m.p. 290-290.5° dec., infrared absorption[20] at 1610 and 1595 cm.$^{-1}$ (aromatic) and ultraviolet maxima at 258 mμ (ϵ 1.63 x 10^4), 293 mμ (ϵ 1.1 x 10^4) and 386 mμ (ϵ 3.44 x 10^4).

Anal. Calcd. for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.58; H, 4.15; N, 16.96.

Dehydrogenation of by-products of the piperylene-cyclopentenone reaction. A fraction (0.760 g., 5 mmoles) enriched in the minor products (less than 10% IX) from the high temperature diene reaction was dissolved in 7.5 ml. of *p*-cymene containing 225 mg. of 30% palladium on charcoal catalyst. The mixture was refluxed under nitrogen for 24 hr. The catalyst was removed and the mixture condensed by distillation at atmospheric pressure. The residue was chromatographed through neutral alumina.

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22) Determined as a solution in deuterochloroform.

The ketone XIII, eluted with a benzene-petroleum ether mixture and then recrystallized from petroleum ether, amounted to 160 mg. (22%) of yellow prisms, m.p. 48-52°, not depressed with authentic material. The ketone XIV, eluted with benzene and recrystallized from petroleum ether, amounted to 20 mg. (3%), m.p. 97-97.8°, not depressed with authentic material. The infrared spectrum[18] of this material is identical with that of authentic material[7] described below.

4-Methyl-1-indanone. This material was prepared by the method described by Dev.[7] The reaction of α-bromo-*o*-xylene (18.5 g., 0.10 mole) with diethylsodiomalonate (0.10 mole) followed by hydrolysis and decarboxylation afforded 3.47 g. (21%) of the crude acid XV. Cyclization in polyphosphoric acid afforded 0.515 g. of the desired ketone as microprisms from petroleum ether, m.p. 97.5-98.2°, with infrared absorption[18] at 1715, 1605, 1595, 1445 and 1375 cm.$^{-1}$ (lit.[7] m.p. 99-100°). The ultraviolet spectrum[19] has maxima at 208 mμ (ϵ 3.13 x 10^4), 250 mμ (ϵ 1.38 x 10^4) and 296 mμ (ϵ 3050). The NMR spectrum[22] has a series of sharp peaks in the region 2.3-3.0 τ (3H, aromatic hydrogen atoms), an A_2B_2 grouping of peaks in the region 6.9-7.6 τ (4H, methylene hydrogen atoms), and a spike at 7.68 τ (3H, methyl hydrogen atoms).

Addition of piperylene to cyclopentenone. B. At low temperature. A mixture of cyclopentenone (30.1 g., 0.366 mole), piperylene (33 g., 0.486 mole), 2,5-di-*t*-butylhydroquinone (1.5 g.) and 50 ml. of benzene were heated in an autoclave for one week at 85°. The mixture was distilled affording 20 g. of forerun and 22.52 g. (41%) of adduct, b.p. 92-100° at 10 mm. Analysis[17] showed that the *cis* ketone VIII was 68% of the products and the *trans* ketone IX amounted to 15%. The major component (VIII) could not be appreciably enriched by fractional distillation as it appeared to equilibrate readily to the ketone IX. A pure sample of the *ketone VIII* was obtained from the mixture by vapor phase chromatography.[17] This material had infrared absorption[18] at 1740 (cyclopentanone carbonyl), 1650 (weak, double bond in *cis* fused ring), 1455 and 1365 cm.$^{-1}$ (methyl group), with only weak end absorption (ϵ 650 at 210 mμ) in the ultraviolet spectrum.[19] The NMR spectrum[18] shows a sharp unresolved peak at 4.43 τ (2H, vinyl hydrogen atoms), broad, slightly resolved absorption between 7.2-8.6τ (9H, methylene and methine hydrogen atoms) and a doublet centered at 8.76τ (3H, methyl hydrogen atoms, $J = 7.1$ c.p.s.).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39; M.W., 150. Found: C, 80.01; H, 9.40; M.W., 150 (mass spectrum).

When the pure ketone VIII (120 mg., 0.80 mmoles) was dissolved in five times its volume of triethylamine and heated overnight at 120° complete[17] equilibration to the *trans* ketone took place. The ketone IX was isolated by washing an ether solution of the equilibration mixture with dilute hydrochloric acid followed by evaporation and distillation. The ketone obtained (93 mg., 77%) had an infrared spectrum[18] identical with that described previously for IX.

cis 7-Methyl-cis-hexahydroindanone (XI). - The mixture of products (1.00 g., 6.7 mmoles) obtained in the low temperature reaction described above were dissolved in ethyl acetate and hydrogenated in the presence of 15 mg. of 5% palladium on charcoal catalyst at atmospheric pressure. Hydrogen uptake amounted to 153 cc. (theor., 149 cc.).

The catalyst was removed and the solution concentrated to a small volume. Analysis of the mixture[17] indicated that the ratio of isomers formed was the same as in the starting unsaturated material. The major component (XI) was collected by vapor phase chromatography. It had infrared absorption[18] at 1735, (cyclopentanone carbonyl), 1450 and 1375 cm.$^{-1}$ (methyl group). The NMR spectrum[18] has broad absorption between 7.6-9.1 τ with sharp peaks in the region 7.85-7.95 τ and the methyl doublet centered at 8.78 τ (J= 6.1 c.p.s.).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59; M.W., 152. Found: C, 78.72; H, 10.59; M.W., 152 (mass spectrum).

trans 7-Methyl-*trans*-hexahydroindanone XII. - An enriched sample (0.9204 g., 6.1 mmoles) of the ketone IX was hydrogenated at atmospheric pressure in 20 ml. of ethyl acetate in the presence of 70 mg. of 5% palladium on charcoal catalyst. When 111% (154 cc.) of the theoretical amount of hydrogen was absorbed the reaction ceased. The catalyst was removed and the mixture was concentrated and distilled through a short-path still (b.p. ~ 105° at 20 mm.) to give 0.687 g. (74%) of a clear liquid which was greater than 95% one isomer. The pure ketone XII was isolated by vapor phase chromatography.[17] This material had infrared absorption[18] at 1740 (carbonyl), 1450 and 1370 cm.$^{-1}$ (methyl) and ultraviolet absorption[19] at 238 mμ (ϵ 112) and 294 mμ (ϵ 34). The NMR spectrum[18] has broad, poorly resolved absorption in the region 7.6-9.1 τ ; the split methyl function appears as an unsymetrical doublet centered at 8.88 τ (J= 4.2 c.p.s.).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59; M.W., 152. Found: C, 78.64; H, 10.61; M.W., 152 (mass spectrum).

Equilibration Studies. - Pure samples of each of the cis-trans isomers studied were dissolved in four times their volume of triethylamine. The solutions were sealed in ampules and were heated in a 100° bath until each isomer of each pair afforded equilibrium mixtures which agreed to within 1% as analyzed by vapor phase chromatography.[17] Standard mixtures of the isomers were used to check the accuracy of the method. The maximum error in this method is ± 2%.

Acid treatment of 7-methyl-3a, 4, 7, 7a-tetrahydroindanone. The ketone IX (0.424 g., 2.92 mmoles) was dissolved in 5 ml. of a one molar solution of sulfuric acid in benzene-acetic acid (1:2). The mixture was sealed in an ampule and was heated at 125° for 18 hr. The mixture was treated with 50 ml. of petroleum ether (b.p. 30-60°) and 25 ml. of cold 20% sodium hydroxide solution. The phases were well mixed and the organic layer was washed with water and dried. Concentration of the solution followed by distillation afforded a liquid (93 mg., 23%), b.p. ca. 130-140° at 20 mm. Analysis[17] of the mixture indicated two products in a ratio of 85:15. The distilled mixture had an ultraviolet maximum[19] at 238 mμ. The major component was isolated by vapor phase chromatography. This material had infrared absorption[18] at 1698 (carbonyl), 1640 (double bond), 1450 and 1380 cm.$^{-1}$ (methyl) and was assigned structure XVI.

Bromination of ketone XII followed by dehydrohalogenation. The ketone XII (0.600 g., 3.95 mmoles) was dissolved in 10 ml. of anhydrous ether and treated dropwise with bromine (ca. 0.65 g., 4 mmoles) at 0° such that each drop fell in a colorless solution. The mixture was stirred an additional 10 min. The ether was removed in a stream of nitrogen. The residue was dissolved in petroleum ether and washed with water. Concentration afforded a yellow residue which darkened on standing with the evolution of hydrogen bromide. This material was dissolved in 10 ml. of pyridine and was refluxed under nitrogen for 8 hr. The mixture was then dissolved in ether and separated from the pyridine hydrobromide. It was added dropwise with stirring to 30 ml. of 18% hydrochloric acid. The organic layer was washed with water, sodium bicarbonate solution and again with water. Drying followed by concentration and short-path distillation afforded 0.348 g. (59%) of a pale yellow liquid. Analysis[17] of the mixture indicated that two new products were present in the ratio of 85:15. The major component (XVI) was collected by vapor phase chromatography.[17] The infrared spectrum[18] of this material is identical with that obtained from the major component isolated in the preceding experiment. It had ultraviolet absorption[19] at 238 mμ (ϵ 11,300). The NMR spectrum[18] has groupings of partially resolved peaks in the regions 7.4-8.0τ (7H, allylic hydrogen atoms) and 8.1-8.8τ (4H, non-allylic methlene hydrogen atoms), and a doublet centered at 8.96τ (3H, methyl hydrogen atoms, J= 6.8 c.p.s.).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.65; H, 9.37.

The minor component (XVII) (not identical with the minor component mentioned in the preceding experiment) was isolated by vapor phase chromatography. The infrared spectrum[18] has absorption at 1708 (carbonyl), 1638 (intense, exocyclic double bond), 1425 and 1368 cm.$^{-1}$ (methyl). The ultraviolet spectrum[19] has a maximum at 256 mμ (ϵ 5500).[23]

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23) This material was identified with authentic ketone XVII prepared and characterized by Dr. M. Schellenbaum in these laboratories.

Dehydrohalogenations of the bromoketone by treatment with a lithium chloride-dimethylformamide mixture, with collidine or by simple distillation all gave mixtures which contained predominately[17] the endocyclic unsaturated ketone XVI.

<u>2, 4, 7, 7a-Tetrahydro-3-acetoxy-4-methlindene (XIX).</u> A solution of the ketone IX (4.00 g., 26.7 mmoles), 12 ml. of redistilled acetic anhydride and 90 mg. of *p*-toluenesulfonic acid hydrate was refluxed under nitrogen for 4 hr. The condenser was replaced by a modified Claisen distilling head and 3 ml. of acetic acid-acetic anhydride was removed, b. p. 130-135°. The solution was replenished with acetic anhydride and refluxed for 4 hr. followed by distillation of the acetic acid formed (5.5 ml., b. p. 134-137°). Refluxing of the replenished mixture followed by distillation again (3.5 ml.) left a dark mixture. This mixture was cooled and neutralized with 200 mg. of anhydrous sodium acetate. Petroleum ether (75 ml., b. p. 30-60°) was added and the mixture was treated with saturated sodium bicarbonate solution until all the anhydride had been destroyed. The organic layer was washed with water and dried. Distillation afforded 3.77 g. of a pale yellow liquid, b. p. 112-122° at 12 mm. Analysis[17] of the material indicated the presence of starting material and two new components. The

major component (XIX) was isolated by vapor phase chromatography. This material had infrared absorption[18] at 1755, 1715 (enol acetate), 1643 (double bond), 1455 and 1362 cm.$^{-1}$ (methyl) and ultraviolet maxima[19] at 245 mμ (ϵ 2.1 x 10^{3}) and 307 mμ (ϵ 600), plus high end absorption. The NMR spectrum[18] of this material shows a series of peaks in the region of 4.5τ (2H, vinyl hydrogen atoms), broad partially resolved absorption in the region 6.8-8.3τ including a spike at 7.93τ (14H, methylene, methine and acetyl hydrogen atoms, J 7.1 c.p.s.). A mass spectrum of this material has a small parent peak at mass 192 and a large peak at mass 150 corresponding to loss of ketene. A satisfactory analysis was not obtained.

The 7-methylhydrindanone enol acetate XXI was prepared and isolated in a similar manner. This material had infrared absorption[18] at 1755, 1710 (enol acetate), 1690 (double bond), 1455 and 1360 cm.$^{-1}$ (methyl) and an inflection in the ultraviolet spectrum[19] at 226 mμ (ϵ 2800). The NMR spectrum[18] has complex splitting in the region 7.5-9.0τ with the acetoxyl hydrogen atoms giving a singlet at 7.97τ and the methyl doublet at 8.89τ (J= 6.3 c.p.s.). A mass spectrum of this material has a parent peak at mass 194 and a large peak at mass 152. A satisfactory analysis was not obtained.

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17) A gas chromatography column packed with Dow Corning Silicone Fluid No. 710 on 60-80 mesh firebrick was employed for this analysis.

18) Determined as a solution in carbon tetrachloride.

19) Determined as a solution in 95% ethanol.

20) Determined as a suspension in potassium bromide.

21) W. S. Johnson, C. E. Davis, R. H. Hunt and G. Stork, J Am. Chem. Soc., 70, 3021 (1948).

22) Determined as a solution in deuterochloroform.

23) This material was identified with authentic ketone XVII prepared and characterized by Dr. M. Schellenbaum in these laboratories.

APPENDIX I

THE STEREOSELECTIVE SYNTHESIS OF ALPHA-SUBSTITUTED ALPHA, BETA-UNSATURATED ESTERS

THE STEREOSELECTIVE SYNTHESIS OF ALPHA-SUBSTITUTED ALPHA, BETA-UNSATURATED ESTERS

It was of interest to study the ability of methyl 2-methyl-2, 4-pentadienoate (Ib) to undergo a Diels-Alder reaction.[1] As this compound was unknown it was necessary to develop a synthesis of this material. The synthesis of the acid IIa[2] and of similar trans α, β-unsaturated acids[3a] from condensation of malonic acid with an aldehyde appears to be quite general, as even substituted malonic acids can be made to successfully undergo condensation with aromatic aldehydes[3b] to afford the corresponding α-alkyl α, β-unsaturated acids. The somewhat severe conditions employed in such reactions, coupled with the sensitivity of diene systems such as IIa to polymerization led us to explore the synthesis of such systems by the Wittig reaction.[4]

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(b) U. Schollkopf, Angew. Chem., 71, 260 (1959).
(c) S. Trippett in R. A. Raphael, E. C. Taylor and H. Wynberg, "Advances in Organic Chemistry, Methods and Results," Vol. 1 Interscience Publishers, Inc., New York, N. Y., 1960, pp. 83-102.

The ylid IIIb can be easily prepared by reaction of methyl α-bromopropionate with triphenylphosphine followed by treatment with potassium hydroxide.[4a] This ylid reacts spontaneously with acrolein to afford the ester Ib. This material exhibited a single peak on gas chromatography and afforded a single crystalline acid Ia on saponification. Esterification of this acid with diazomethane regenerated the ester Ib. That it was the desired trans system I was shown by a comparison of the ultraviolet spectra of the acid Ia and ester Ib, which have ma~~xi~~ma at 251 mμ (ε 23,000) and 253 mμ (ε 24,300), respectively, with the spectra of IIa and IIb which show corresponding absorption at 244 mμ (ε 24,000) and 247 mμ (ε 20,600).

As the relative steric size of the methyl group to the carbomethoxy group is not sufficient to explain the reason for formation of only one isomer in the above case, it was decided to explore this reaction further to see if the stereochemical outcome of this reaction could be predicted.

The results obtained here as well as previous reports[4a, 5] that unsaturated esters derived from the ylid IIIc possessed the configuration in which the carboalkoxy group was trans to the larger group at the beta-carbon atom suggested that this was a general phenomenon and that this reaction would be expected to parallel the stereochemical outcome of the Perkin and related reactions.[3, 6]

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5) G. Wittig and U. Schollkopf, Chem. Ber., 87, 1318 (1954).

6) H. E. Zimmerman and L. Ahramjian, J. Am. Chem. Soc., 81, 2086 (1959).

Since methyl angelate (IV) and methyl tiglate (V) have thoroughly established configurations[7] the synthesis of this system by the reaction of the ylid IIIb with acetaldehyde was investigated.

This reaction proceeded to give methyl tiglate (V) containing no more than 3.5% of methyl angelate (IV). The less stable[7] methyl angelate was found not to isomerize under the conditions of the reaction and its workup.

The difference in steric interactions involved in the formation of the intermediate betaines VI and VII appears to be too small to account for the degree of stereoselectivity observed. A better explanation of this phenomenon would be the <u>reversible</u> formation of the intermediates VI and VII with the reaction proceeding to completion over the less energetic route.

The results of the reaction can be explained by assuming that the transition state VIII requires more activation energy than the corresponding transition state IX. In the latter case overlap between the pi orbitals of the carbonyl group and the incipient carbon-carbon double bond would be expected to lower the energy of the transition state. However, this overlap is possible only when the carbonyl function lies in the plane of the developing double bond. It can be seen that in the transition state VIII steric interaction between the β-methyl group and the carbomethoxy function would offer interference to this coplanarity requirement. Thus, one would

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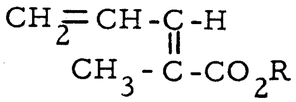
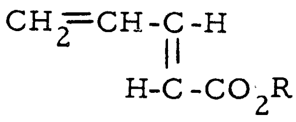
7) R. E. Buckles, G. V. Mock and L. Locatell, Jr., Chem. Revs., 55, 659 (1955).



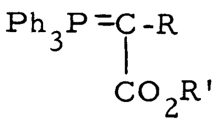
$CH_2{=}CH{-}C(H){=}C(CH_3){-}CO_2R$

Ia $R = H$
b $R = CH_3$



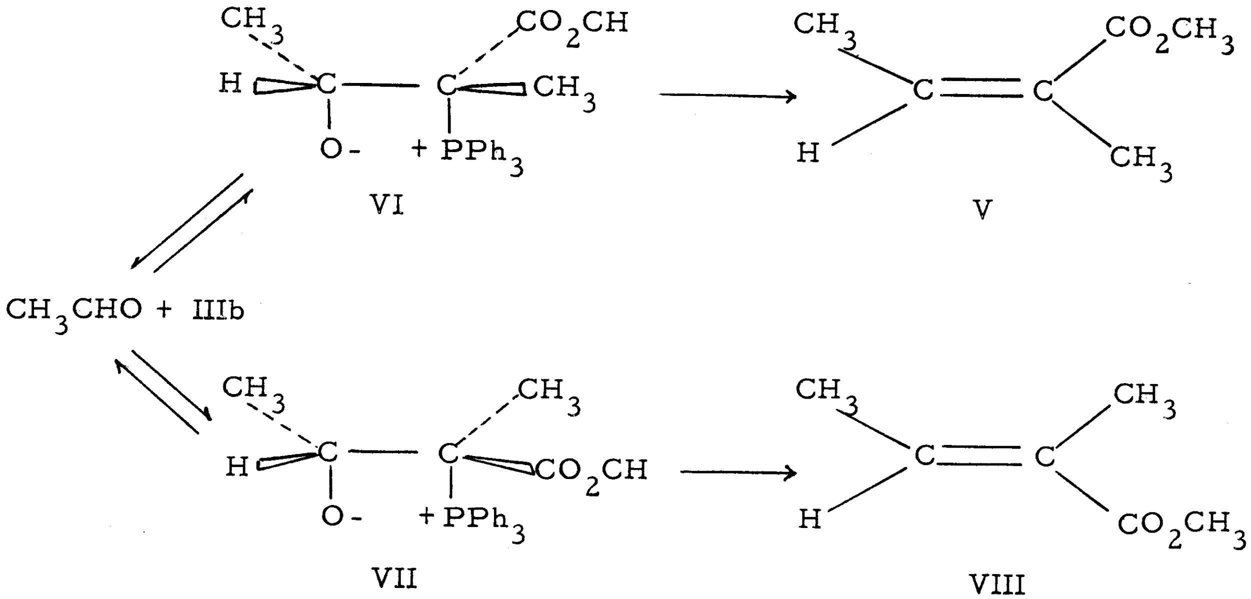
$CH_2{=}CH{-}C(H){=}C(H){-}CO_2R$

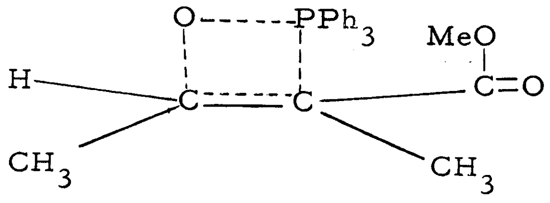
IIa $R = H$
b $R = CH_3$



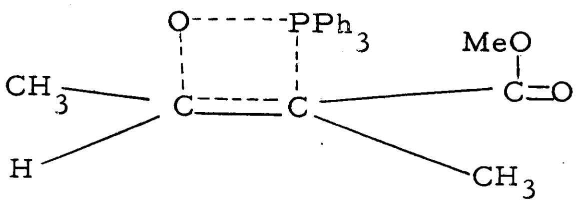
$Ph_3P{=}C(R){-}CO_2R'$

IIIa $R = H$ $R' = CH_3$
b $R = CH_3$ $R' = CH_3$
c $R = H$ $R' = C_2H_5$





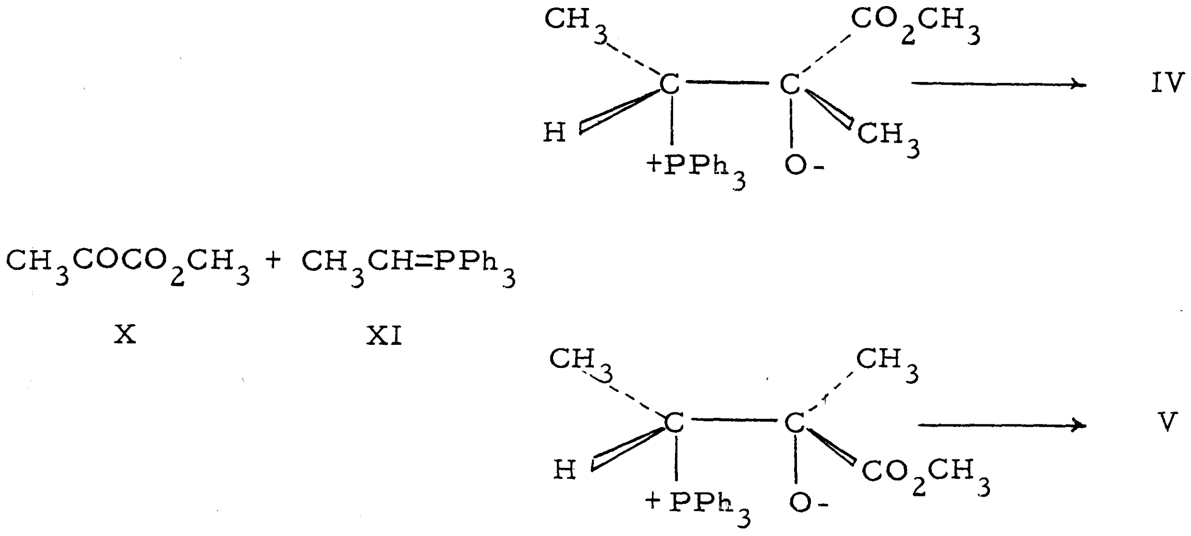
IX



VIII

expect that the activation energy required for the transition VI to IV would be greater than for the corresponding conversion VII to V.[8]

If these assumptions are correct then reactions between highly reactive ylids and carbonyl compounds should oppose reversible formation of the intermediate betaines[9] and, thus, afford less stereoselectivity in product formation. To test this prediction the reaction between methyl pyruvate (X) and triphenylphosphinethylidene (XI) was investigated. In contrast to the high degree of selectivity obtained in the reaction between acetaldehyde and the ylid IIIb this reaction afforded an ester mixture composed of 68% methyl tiglate and 32% methyl angelate.



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8) For a discussion of a comparable situation, see H. E. Zimmerman and L. Ahramjian, J. Am. Chem. Soc., 82, 5459 (1960).

9) For a discussion and experimental evidence that the betaine from triphenylphosphinemethylene and benzaldehyde is not formed reversibly see G. Wittig, H. Weigmann and M. Schlosser, Chem. Ber., 94, 676 (1961).

EXPERIMENTAL[10]

<u>2,4-Pentadienoic Acid (IIa).</u> - The reaction of 118 g. (0.53 mole) of potassium metabisulfite, 29 g. (0.52 mole) of acrolein and 52 g. (0.50 mole) of malonic acid in 200 ml. of water as previously described[2] afforded the crude dienoic acid which was recrystallized from an ether-petroleum ether mixture. The pure acid separated as 9.78 g. of pale yellow needles, m.p. 71.5-72.5° (lit.[2] 72°), which exhibited infrared absorption[11] at 3000 cm.$^{-1}$ (broad, assoc. O–H), at 1690 cm.$^{-1}$ (conj. carboxyl C=O), at 1635 cm.$^{-1}$ (conj. C=C), at 930 cm.$^{-1}$ with a shoulder at 950 cm.$^{-1}$ (<u>trans</u> CH=CH) and at 875 cm.$^{-1}$ (conj. CH_2=CH). The acid had an ultraviolet maximum[12] at 244 mμ (ϵ 24,000). Concentration of the mother liquors afforded an additional 4.09 g. of crude acid, m.p. 66.5-69.5° (total yield 13.87 g. or 27.4%).

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[10] All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with either a Baird, model B, or a Perkin-Elmer, model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 11MS. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

[11] Determined as a solution in chloroform.

[12] Determined as a solution in 95% ethanol.

An 8.4-g. (0.10 mole) sample of the acid (IIa) in ether was allowed to react with a slight excess of diazomethane. After the resulting solution had been washed successively with aqueous sodium bicarbonate and water, dried over magnesium sulfate and concentrated, distillation of the residue separated 5.85 g. (61%) of the methyl ester IIb, b.p. 36-38° (10 mm.) (lit.[13] 77-80° at 25 mm.), n_D^{23} 1.4833, with infrared absorption[14] at 1720 cm.$^{-1}$ (conj. ester $C=O$), at 1645 and 1605 cm.$^{-1}$ (conj. $C=C$), at 925 cm.$^{-1}$ (*trans* $CH=CH$) and at 870 cm.$^{-1}$ (conj. $CH_2=CH$) and an ultraviolet maximum[12] at 247 mμ (ε 20,600). A gas chromatogram[15] of the ester exhibits a single peak.

This was also prepared in 30% yield from the reaction of the ylid IIIa[4a] with acrolein.

Methyl 2-methyl-2,4-pentadienoate (Ib). - The reaction of 209 g. (0.80 mole) of triphenylphosphine with 126 g. (0.75 mole) of methyl α-bromopropionate in 960 ml. of benzene followed by reaction of the crude phosphonium salt with aqueous potassium hydroxide as previously described[4a] yielded the crude phosphorane IIIb, m.p. 146-152°, yield 111.3 g. (44%). Recrystallization of a 91-g. portion of this material from an ethyl acetate-petroleum ether mixture separated 83 g. of the pure phos-

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13) E. P. Kohler and F. R. Butler, J. Am. Chem. Soc., 48, 1036 (1926).

14) Determined as a solution in carbon tetrachloride.

15) A column packed with 1,2,3-tris-(2-cyanoethoxy) propane suspended on ground firebrick was employed.

phorane IIIb, m.p. 152-154.5° (lit.[4a] 152-153°), which exhibited broad, intense infrared absorption[11] at 1600 cm.$^{-1}$ with an ultraviolet maximum[12] at 226 mμ (ε 26,000) and a series of low intensity peaks (ε 4000 to 4900) in the region 260-275 mμ.

To a solution of 64.0 g. (0.184 mole) of the ylid IIIb in 110 ml. of methylene chloride was added, dropwise and with stirring, 12.6 g. (0.225 mole) of acrolein. After the resulting mixture had been refluxed for 3.5 hr., the solution was concentrated by the distillation of approximately half of the methylene chloride from the mixture through a 30-cm. Vigreaux column. The residual solution was diluted with 250 ml. of petroleum ether and filtered to remove the triphenylphosphine oxide which separated. After the precipitated triphenylphosphine oxide had been washed with an additional 100 ml. of petroleum ether, the combined organic solutions were concentrated. Distillation of the residue afforded 13.78 g. (60%) of the ester, b.p. 50-50.5° (7-8 mm.), n_D^{26} 1.4882. The gas chromatogram[16] exhibited a major peak corresponding to 96% of the volatile material. A pure sample was collected from the chromatograph for analysis. The material had infrared absorption[14] at 1715 cm.$^{-1}$ (conj. ester C=O) at 920 cm.$^{-1}$ (CH_2=CH) with an ultraviolet maximum[12] at 253 mμ (ε 24,300).

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.59; H, 8.04.

A solution of 1.382 g. (0.011 mole) of the methyl ester Ib in 15 ml.

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[16] A column packed with Dow Silicone Fluid No. 550 suspended on ground firebrick was employed.

of a 6% solution of sodium hydroxide in methanol was refluxed for 2 hr. under a nitrogen atmosphere and then concentrated under reduced pressure and diluted with 35 ml. of water. The resulting solution was acidified at 0° and then extracted with chloroform. After the extract had been washed with water, dried over magnesium sulfate and concentrated, the crude solid residue (1.12 g.) was recrystallized from an ether-petroleum ether mixture. The acid Ia separated as white needles, m.p. 60.4-63°, yield 0.82 g. (67%). Sublimation of this material under reduced pressure afforded the pure acid Ia, m.p. 63.8-65°, which exhibited infrared absorption[14] at 3000 cm.$^{-1}$ (broad, assoc. O-H), at 1685 cm.$^{-1}$ (conj. carboxyl C=O) and at 925 cm.$^{-1}$ (CH_2=CH) and an ultraviolet maximum[12] at 251 mμ (ε 23,000).

Anal. Calcd. for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 63.99; H, 7.19.

An ethereal solution of 1.03 g. (0.0090 mole) of the acid Ia was treated with a slight excess of diazomethane and the crude product was isolated in the usual manner. Distillation afforded 0.761 g. (67%) of the methyl ester Ib, b.p. 48-48.5° (7 mm.), n_D^{25} 1.4901, which had infrared and ultraviolet absorption identical with the previously described sample.

Methyl Tiglate (V). - An authentic sample of tiglic acid,[17] which had infrared bands[14] at 2950 cm.$^{-1}$ (broad, assoc. O-H) at 1680 cm.$^{-1}$ (conj. carboxyl C=O) and at 1640 cm.$^{-1}$ (conj. C=C), an ultraviolet maxi-

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[17] Aldrich Chemical Company, Inc., Milwaukee, Wisconsin.

mum[12] at 212 mμ (ϵ 11,400), was converted to the methyl ester V by reaction with diazomethane in the usual manner. After distillation through a short-path still, the ester V, n_D^{26} 1.4344 (lit.[17] n_D^{20} 1.4370), exhibited infrared absorption[15] at 1720 cm.$^{-1}$ (conj. ester C=O) and at 1635 cm.$^{-1}$ (conj. C=C) with an ultraviolet maximum[12] at 215 mμ (ϵ 11,500). The gas chromatogram[18] of the ester exhibits a single peak.

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18) A column packed with 20 M Carbowax suspended on ground firebrick was employed.

<u>Methyl Angelate (IV).</u> - A sample of 2-bromo-<u>trans</u>-2-butene, b.p. 39-41.5° (133-137 mm.), $n_D^{25.5}$ 1.4552, containing[18] 98% of the desired isomer, was prepared as previously described.[19] A solution of 40.6 g. (0.30 mole) of the bromobutene in 100 ml. of ether was added, dropwise and with stirring under a nitrogen atmosphere, to a suspension of 4.2 g. (0.61 mole) of lithium in 150 ml. of ether cooled in an ice bath. The resulting solution of the organolithium compound was poured onto a slurry of excess Dry Ice in 200 ml. of ether. The resultant mixture was allowed to warm to room temperature and then diluted with aqueous hydrochloric acid. After the ether layer had been separated and extracted with sodium bicarbonate, the bicarbonate solution was acidified and extracted with ether. The ethereal solution was dried over magnesium sulfate and concentrated to leave 12.3 g. of crude angelic acid, m.p. 38-43°, which

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19) H. O. House and R. S. Ro, J. Am. Chem. Soc., <u>80</u>, 2428 (1958) and references therein.

was recrystallized to separate 10.4 g. (35%) of angelic acid as white prisms, m.p. 40-43° (lit.[7] 45.0-45.5°), with infrared absorption[14] at 2950 cm.$^{-1}$ (broad, assoc. O-H), at 1685 cm.$^{-1}$ (conj. carboxyl C=O) and at 1640 cm.$^{-1}$ (conj. C=C) and an ultraviolet maximum[12] at 213 mμ (ϵ 7,400). A 5.0-g. (0.05 mole) sample of this acid, after esterification with diazomethane in the usual manner, yielded 4.48 g. (79%) of ester IV, b.p. 45° (26-28 mm.), $n_D^{25.5}$ 1.4292 (lit.[7] b.p. 127.6-128°, n_D^{20} 1.4321) which contained[18] more than 98% of methyl angelate.[20] The ester IV has infrared bands[14] at 1715 cm.$^{-1}$ (conj. ester C=O) and at 1645 cm.$^{-1}$ (conj. C=C) with an ultraviolet maximum at 216 mμ (ϵ 9,200).

Reaction of the Phosphorane IIIb with Acetaldehyde. - To a solution of 30.0 g. (0.086 mole) of the ylid IIIb in 100 ml. of methylene chloride was added, dropwise under a nitrogen atmosphere, 7.8 g. (0.18 mole) of acetaldehyde. The resulting solution was allowed to stand overnight and then concentrated, diluted with 200 ml. of petroleum ether and filtered to remove the precipitated triphenylphosphine oxide. Distillation of the filtrate separated 8.84 g. (90%) of a product mixture, b.p. 68-69° (62-65 mm.), n_D^{25} 1.4274, containing[18] 93.5% methyl tiglate and 3.2% methyl angelate corresponding to an ester mixture containing 96.5% methyl tiglate and 3.5% methyl angelate. Fractional distillation of this mixture separated a sample of pure methyl tiglate, $n_D^{25.5}$ 1.4337, which had in-

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20) The substantial contamination with methyl tiglate noted in the previous preparation [A. S. Dreiding and R. J. Pratt, J. Am. Chem. Soc., 76, 1902 (1954)] of angelic acid by this procedure was almost certainly due to the use of impure bromo olefin as the starting material (see ref. 19).

frared absorption identical with that of the authentic sample.

To establish that methyl angelate would be stable under the conditions of this preparation, a solution of 3.94 g. (0.0345 mole) of methyl angelate, 9.6 g. (0.0345 mole) of triphenylphosphine oxide and 3 mg. of the ylid IIIb in 25 ml. of methylene chloride was refluxed for 4 hr. and then worked up as previously described. The recovered methyl angelate, 2.15 g. (55%), b.p. 43.5-44.5° (26 mm.), n_D^{26} 1.4281, contained[15] less than 1% of methyl tiglate.

Reaction of the Phosphorane XI with Methyl Pyruvate (X). - Reaction of 39 g. (0.15 mole) of triphenylphosphine with 22 g. (0.20 mole) of ethyl bromide in 50 ml. of benzene at 135° in an autoclave for 20 hr. followed by recrystallization of the precipitated phosphonium salt from water and subsequent drying afforded 49.5 g. (89%) of ethyltripehnylphosphonium bromide as white prisms, m.p. 209-210.5° (lit.[21] 203-204°).

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21) G. Wittig and D. Wittenberg, Ann., 606, 1 (1957).

An ethereal solution (90 ml.) containing 0.105 mole of phenyllithium was added, with stirring in a nitrogen atmosphere, to a suspension of 40.0 g. (0.108 mole) of the phosphonium salt in 200 ml. of ether. After the addition was complete, the resulting red solution was stirred for 1 hr. at which time the mixture gave a negative Gilman color test for phenyllithium. The ethereal solution of the ylid was added, dropwise and with stirring in a nitrogen atmosphere, to a solution of 9.0 g. (0.088 mole) of methyl pyruvate in 10 ml. of ether until the red color of the mixture persisted in the reaction mixture. At this point the reaction mixture was heated to reflux, the remainder of the ylid solution was added, and the resulting mixture was refluxed overnight with stirring. The bulk of the ether was distilled from the pasty reaction mixture and 400 ml. of tetrahydrofuran was added. The resulting mixture was refluxed for 36 hr. under a nitrogen atmosphere and again concentrated to about 75 ml. by distillation of the tetrahydrofuran through a 30-cm. Vigreaux column. The reaction mixture was diluted with ether and the ethereal solution was separated from an insoluble semisolid and distilled. The ester mixture obtained, b.p. 34-36° (25 mm.), $n_D^{24.5}$ 1.4396-1.4405, amounted to 2.10 g. (21%) and contained[16] 68% methyl tiglate and 32% methyl angelate. Samples collected from the chromatograph[16] were identified by comparison of their spectra with the spectra of authentic samples.

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1) See Section II, Part I of this thesis.

2) I. E. Muskat, B. C. Becker and J. S. Lowenstein, J. Am. Chem. Soc., 52, 326 (1930).

3) (a) J. R. Johnson, Org. Reactions, 1, 210 (1942).
(b) W. J. Gensler and E. Berman, J. Am. Chem. Soc., 80, 4949 (1958).

4) (a) O. Isler, H. Gutmann, M. Montavon, R. Ruegg, G. Ryser and P. Zeller, Helv. Chim. Acta, 40, 1242 (1957).
(b) U. Schollkopf, Angew. Chem., 71, 260 (1959).
(c) S. Trippett in R. A. Raphael, E. C. Taylor and H. Wynberg, "Advances in Organic Chemistry, Methods and Results," Vol. 1 Interscience Publishers, Inc., New York, N. Y., 1960, pp. 83-102.

5) G. Wittig and U. Schollkopf, Chem. Ber., 87, 1318 (1954).

6) H. E. Zimmerman and L. Ahramjian, J. Am. Chem. Soc., 81, 2086 (1959).

7) R. E. Buckles, G. V. Mock and L. Locatell, Jr., Chem. Revs., 55, 659 (1955).

8) For a discussion of a comparable situation, see H. E. Zimmerman and L. Ahramjian, J. Am. Chem. Soc., 82, 5459 (1960).

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11) Determined as a solution in chloroform.

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15) A column packed with 1, 2, 3-tris-(2-cyanoethoxy) propane suspended on ground firebrick was employed.

16) A column packed with Dow Silicone Fluid No. 550 suspended on ground firebrick was employed.

17) Aldrich Chemical Company, Inc., Milwaukee, Wisconsin.

18) A column packed with 20 M Carbowax suspended on ground firebrick was employed.

19) H. O. House and R. S. Ro, J. Am. Chem. Soc., 80, 2428 (1958). and references therein.

20) The substantial contamination with methyl tiglate noted in the previous preparation [A. S. Dreiding and R. J. Pratt, J. Am. Chem. Soc., 76, 1902 (1954).] of angelic acid by this procedure was almost certainly due to the use of impure bromo olefin as the starting material (see ref. 19).

21) G. Wittig and D. Wittenberg, Ann., 606, 1 (1957).

CYCLOPENTANE-1, 2-DIONE

In the search for synthetic methods of construction of polyhydroindanone systems it became of interest to study the ability of cyclopentane-1, 2-dione (I) to undergo a Micheal reaction. Such a reaction employing methyl vinyl ketone would afford a synthetic approach to the enedione II, which itself could serve as an intermediate in the synthesis of compounds related to gibberellic acid.[1]

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[1] See Section II, Part I of this thesis.

The enolic cyclopentane-1, 2-dione (I) has been prepared by acid decarbethoxylation of the diester III.[2] In our hands, however, this method gave predominately 2-ethoxycyclopentenone (IV). This product presumably arises by esterification of the dione I with the ethanol produced in hydrolysis. Continuous extraction of the acidic reaction mixture with ether for a relatively long time permitted this secondary reaction to occur and the product to escape the hydrolyzing mixture.

The synthesis of cyclopentane-1, 2-dione by the method of Acheson[3] gave more desirable results. In this procedure a -bromocyclopentanone was hydrolyzed and oxidized to the desired diketone I in moderate yield (35%).

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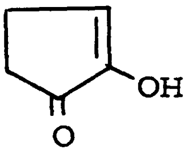
[2] G. Esse and E. Bucking, Ann., 563, 31 (1949).

[3] R. M. Acheson, J. Chem. Soc., 4232 (1956).

Micheal reaction of cyclopentane-1, 2-dione with methyl vinyl ketone in the presence of triethylamine gave the addition product V. This material would be expected to undergo cyclodehydration to give the desired enedione II. Further studies in this area were not pursued.



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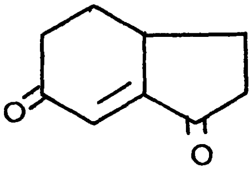

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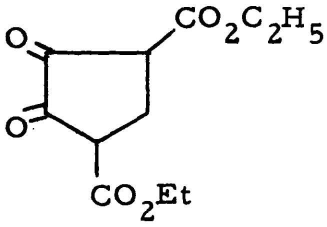

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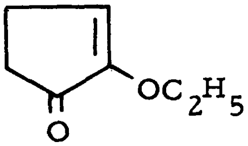

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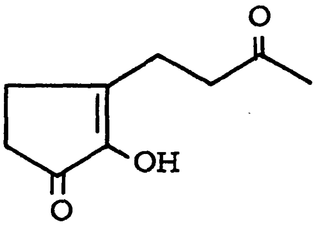

V

EXPERIMENTAL[4]

Cyclopentane-1, 2-dione (I).[3] A solution of cyclopentanone (180 g., 2.14 moles) in a mixture of 100 ml. of acetic acid and 400 ml. of water water was heated to 45°. To the stirred mixture was added bromine (340 g., 2.12 moles) over a period of 20 min., the temperature being maintained at 40-45° by cooling in an ice bath. Upon complete addition the temperature rose to 50-56° before the reaction was complete. The mixture was then neutralized with 205 g. (1.9 moles) of sodium carbonate (caution, do not make the mixture basic). The lachrymatory, crude α-bromocyclopentanone which separated was washed twice with 100-ml. portions of saturated sodium chloride solution and amounted to 283 g. (81.5%).

The crude bromide (278 g., 178 moles) was stirred with 1700 ml. of water on a steam bath until solution was complete. To this mixture was added in a stream a hot (100°) solution of 770 g. (2.95 moles) of ferric chloride hexahydrate in 375 ml. of water. The mixture was allowed to stand overnight at room temperature and then was saturated with 550 g. of ammonium sulfate. The mixture was then continuously extracted with

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4) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with a Baird, model B, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 11MS. The microanalyses were performed by the Scandinavian Microanalytical Laboratory. Unless otherwise stated magnesium sulfate was employed as a drying agent. The NMR spectra were determined with a Varian, model A-60, NMR spectrometer.

ether for 12 days, the ether extract periodically being removed and replaced by additional ether. The ether extracts were dried and concentrated to a black oil which was distilled through a short-path, air-cooled still to give the crude diketone (90.4 g., 54%), b.p. 81-90° at 7 mm., which readily crystallized. Recrystallization of this material from an ether-petroleum ether mixture gave 50.39g.(30%) of *cyclopentane-1,2-dione* as coarse, tan prisms, m.p. 54.5-56.0°, (lit.[3] m.p. 55-56°), with infrared absorption[5] at 3500 and 3350 (unassoc. and assoc. OH), 1710 (cyclopentenone C=O) and 1654 cm.$^{-1}$ (C=C) and ultraviolet absorption[6] at 253 mμ (ε 9000). An additional 10.92 g. (m.p. 51-54°) of the diketone was obtained from the filtrate. The over-all yield from α-bromocyclopentanone amounted to 61.31 g. (35%). Caution must be used in handling cyclopentane-1,2-dione as it leaves black stains on the skin. These stains do not appear immediately but remain for a long time.

Decarbethoxylation of 1,4-dicarbethoxycyclopentane-2,3-dione III.[2] The diester-diketone III (82 g., 0.34 mole) was treated with 330 g. of 20% aqueous sulfuric acid solution. The mixture was refluxed under nitrogen for 2.5 hr. After cooling to room temperature the mixture was saturated with ammonium sulfate and was continuously extracted with ether under a nitrogen atmosphere for 3.5 days. The extract was dried and

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5) Determined as a solution in chloroform.

6) Determined as a solution in 95% ethanol.

concentrated to a black liquid. Distillation afforded 14.29 g. of a liquid, b.p. 114-119° at 38 mm. Vapor phase chromatography[7] indicated the presence of cyclopentane-1,2-dione (~30%) and of another component of longer retention time corresponding to about 70% of the mixture. The major component identified as 2-ethoxycyclopentenone (IV) was isolated by vapor phase chromatography and had infrared absorption[8] at 1725 (cyclopentenone C=O) and 1625 cm.$^{-1}$ (C=C), an ultraviolet maximum[6] at 252 mμ (ϵ 8150). The NMR spectrum[8] (60 mc.) has a triplet (J= 2.8 c.p.s.) centered at 3.68τ (1H, vinyl hydrogen atom), a quartet (J= 7.1 c.p.s.) centered at 6.1τ (2H, methylene hydrogens of ethyl group), a complex A_2B_2 pattern in the region 7.4-7.9τ (4H, methylene hydrogen atoms of 5-membered ring) and a triplet (J= 7.1 c.p.s.) centered at 8.66τ (3H, hydrogens of methyl group).

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99; M.W., 126. Found: C, 66.42; H, 8.10; M.W., 126 (mass spectrum).

1-(2,3-dioxo-1-cyclopentyl)-3-butanone (V). - To a stirred solution of cyclopentane-1,2-dione (3.00 g., 0.0306 mole) and freshly distilled methyl vinyl ketone (2.15 g., 0.0307 mole) in 10 ml. of ether was added 2.00 ml. of triethylamine. The mixture was stirred at room tem-

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[7] A gas chromatography column packed with Dow Corning Silicone Fluid No. 710 on 60-80 mesh firebrick was employed for this analysis.

[8] Determined as a solution in carbon tetrachloride.

perature under nitrogen for 2.5 hr., the solution gradually becoming darker. The solvent was removed under reduced pressure and the residue was distilled through a short-path still to give 2.8950 g. (b.p. 140-150° at 0.6 mm.) of the Micheal addition product (V) as a crude, brown liquid which slowly solidified. Recrystallization of this material from an ether-cyclohexane mixture (Norit) afforded 1.66 g. (32%) of pale yellow prisms, m.p. 42-45°. An analytical sample obtained by recrystallization and sublimation had m.p. 47.2-48.2° with infrared absorption[8] at 3500 and 3350 (unassoc. and assoc. OH), 1700-1720 (cyclopentenone and side chain C=O) and 1655 cm.$^{-1}$ (C=C), and an ultraviolet maximum[6] at 260 mμ (ε 10,300). The NMR spectrum[5] (60 mc.) has a broad peak at 3.19 τ (1H, enol hydrogen atom), a series of peaks in the region 3.0-3.7τ (4H, methylene hydrogen atoms) and a singlet peak at 7.81τ (3H, methyl hydrogen atoms).

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19; M.W., 168. Found: C, 64.26; H, 7.17; M.W., 168 (mass spectrum).

REFERENCES

1) See Section II, Part I of this thesis.

2) G. Esse and E. Bucking, Ann., 563, 31 (1949).

3) R. M. Acheson, J. Chem. Soc., 4232 (1956).

4) All melting points are corrected and all boiling points are uncorrected. The infrared spectra were determined with a Baird, model B, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 11MS. The microanalyses were performed by the Scandinavian Microanalytical Laboratory. Unless otherwise stated magnesium sulfate was employed as a drying agent. The NMR spectra were determined with a Varian, model A-60, NMR spectrometer.

5) Determined as a solution in chloroform.

6) Determined as a solution in 95% ethanol.

7) A gas chromatography column packed with Dow Corning Silicone Fluid No. 710 on 60-80 mesh firebrick was employed for this analysis.

8) Determined as a solution in carbon tetrachloride.

BIOGRAPHICAL NOTE

Gary Henry Rasmusson, son of Alice Henry Rasmusson and the late Rudolf M. Rasmusson, was born on August 2, 1936 in Clark, South Dakota. After graduating from Clark High School in 1954 he attended St. Olaf College in Northfield, Minnesota where he received a B. A. degree on June 8, 1958. Since September of 1958 he has been a graduate student at Massachusetts Institute of Technology.

The author is a member of Phi Beta Kappa and of the American Chemical Society.

He was married to the former Nancy Elaine Torkelson on June 7, 1958. Their son, Randall Lee, was born on August 1, 1960.