m.p. was unchanged (98.5–101°). Acetylation of the synthetic material yielded an acetate (see below) identical with that of dihydrovisnaginone: m.p. and mixed m.p. 98–100°.

Absorption spectra of synthetic and "natural" dihydrovisnaginone were determined in approximately 2.5 × 10^{-5} *M* solutions in (a) 95% ethanol and (b) 0.032 *N* sodium hydroxide solution. The absorption spectrum of dihydroallovisnaginone was measured at the same time and in the same way. A Beckman model DU ultraviolet spectrophotometer was used.

The isomeric 4-hydroxy-6-methoxy-5-acetylcoumarane (dihydroallovisnaginone) was isolated from fractions 2 and 3 from the chromatographic separation described above. These were rechromatographed in the same way; the first 40 ml. of eluate yielded 300 mg. of m.p. 100–105°. Mixed with dihydrovisnaginone, the m.p. was depressed to 74–85°. After recrystallization from aqueous methanol the near colorless, centimeter-long needles melted at 106–108°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.18; H, 5.94.

Dihydrovisnaginone Acetate.—A mixture of 4.0 g. of dihydrovisnaginone, 4 g. of anhydrous sodium acetate and 40 ml. of acetic anhydride was refluxed for 5 min. and then heated on the steam-bath for an hour. The reaction mixture was cooled and poured onto ice and the resulting colorless needles collected and recrystallized from aqueous methanol. The product (2.25 g.) melted at 98–100°.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; N, 5.64. Found: C, 62.13; H, 5.60.

Visnaginone (V).—A trace of benzoyl peroxide was added to a mixture of 920 mg. of dihydrovisnaginone acetate and 694 mg. of N-bromosuccinimide in 40 ml. of carbon tetrachloride. The mixture was heated; after about a minute of refluxing a red-brown color appeared and after another half-minute the solution was again colorless and hydrogen bromide began to appear at the condenser outlet. Refluxing was continued for 50 minutes by which time hydrogen bromide evolution had ceased. The mixture was cooled and filtered and the filtrate evaporated in an air stream. The nearly colorless oil which remained (1.34 g.) was heated for 3 hours with 15 ml. of freshly distilled dimethylaniline in a metal-bath held at 195–200°. The brown solution was cooled, diluted with ether and washed with three 30-ml. portions of 3 *N* sulfuric acid. Removal of the ether left a brown oil which was heated on the steam-bath for 30 minutes with a solution of 1.5 g. of potassium hydroxide in 20 ml. of aqueous (1:1) methanol. The solution was diluted with water, acidified and extracted with ether. The ether solution was washed with dilute acid and water, dried and evaporated. The residue was a yellow crystalline material weighing 634 mg. Recrystallization from dilute methanol afforded 444 ml. of bright yellow needles, m.p. 108–109°, not depressed upon admixture with authentic visnaginone. The compound gave a clear green color with alcoholic ferric chloride, identical with that given by visnaginone in a parallel test.

Visnaginone Acetate.—Acetylation of visnaginone with acetic anhydride–sodium acetate yielded the colorless acetate: white needles, m.p. 64.5–65.5°.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 63.07; H, 5.12.

Both the synthetic and natural samples of visnaginone yielded the same acetate (m.p. and mixed m.p.).

Acknowledgment.—The authors gratefully acknowledge the generosity of the Smith, Kline and French Laboratories and the S. B. Penick Company, who have furnished financial support and supplies of some of the materials used in this work.

Analyses were performed by Mrs. Beatrice Kent (U.C.L.A.) and the Clark Microanalytical Laboratories, Urbana, Illinois.

Summary

The total synthesis of visnaginone has been accomplished, starting from phloroglucinol.

A new procedure for the conversion of a coumarane into a coumarone, employing N-bromosuccinimide, has been described.

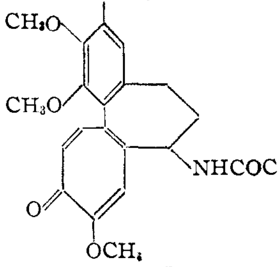
Los Angeles, California Received June 28, 1950

[Contribution from the Department of Chemistry, Washington University]

The Synthesis, Stereochemistry, and Infrared and Ultraviolet Spectra of Several Tricyclic Ketones Homologous with Ketoöctahydrophenanthrene[1]

By C. David Gutsche

As part of a program concerned with the synthesis of colchicine (I) and related compounds several tricyclic ketones of the general structure II have been made in the hope that the methods employed, the compounds themselves, and the infrared and ultraviolet spectra might serve as useful reference points for other syntheses in this series.



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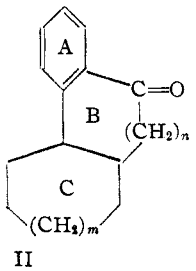

II

Series A [Ring C Six-membered ($m = 1$); Ring B Five-, Six- and Seven-membered ($n = 0, 1, 2$)].—The ketones of series A were prepared by cyclization of *cis*-2-phenylcyclohexanecarboxylic (IIIa), -acetic (IVa), and -propionic (Va) acids and *trans*-2-phenylcyclohexanecarboxylic (IIIb), -acetic (IVb) and -propionic (Vb) acids, the preparation and stereochemistry of which have previously been described.[2]

Interesting differences in the ease of cyclization of the various acids were noted. Under the influence of anhydrous hydrogen fluoride only three of the six acids formed cyclic ketones. *cis*-2-Phenylcyclohexanecarboxylic acid (IIIa) formed 1,2,3,4,4a,9a-hexahydro-9-ketofluorene (VIa),[3] previously described by Cook and Hewett[4] and by

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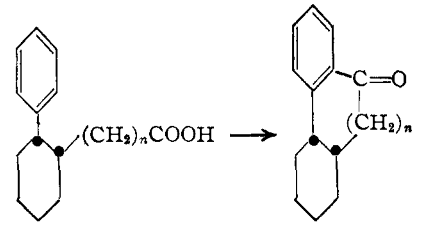
[1] This research was supported in part by a grant from the National Cancer Institute, U. S. Public Health Service.

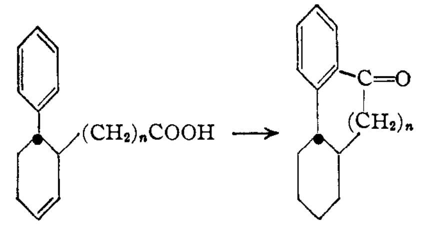
(2) Gutsche, This Journal, 70, 4150 (1948).

(3) We are indebted to Dr. Leonard T. Capell of *Chemical Abstracts* for advice concerning the nomenclature of the tricyclic ketones discussed in this paper.

(4) Cook and Hewett, *J. Chem. Soc.*, 62 (1936).



IIIa (n = 0) VIa (n = 0)
IVa (n = 1) VIIa (n = 1)
Va (n = 2) VIIIa (n = 2)



IIIb (n = 0) VIb (n = 0)
IVb (n = 1) VIIb (n = 1)
Vb (n = 2) VIIIb (n = 2)

Fujise,[5] and *cis*- and *trans*-2-phenylcyclohexaneacetic acids (IVa and IVb) formed *cis*- and *trans*-1,2,3,4,4a,9,10,10a-octahydro-9-ketophenanthrene (VIIa and VIIb) previously synthesized by Cook and his co-workers[6] and by Linstead and his co-workers.[7] On the other hand, *trans*-2-phenylcyclohexanecarboxylic acid (IIIb) and *cis*- and *trans*-2-phenylcyclohexanepropionic acids (Va and Vb) yielded unchanged starting materials. The acids unaffected by anhydrous hydrogen fluoride were smoothly cyclized, however, to 1,2,3,4,4a,9a-hexahydro-9-ketofluorene (VIa) and *cis*- and *trans*-6,7,7a,8,9,10,11,11a-octahydro-5-keto-5*H*-dibenzo [*a*,*c*]cycloheptatriene (VIIIa and VIIIb) by conversion to the acid chlorides followed by treatment with anhydrous aluminum chloride. The failure of Va and Vb to respond to hydrogen fluoride treatment again illustrates the difference in the ease of formation of six- and seven-membered rings.[8] The failure of IIIb to cyclize with hydrogen fluoride is probably due to steric factors, for IIIa with hydrogen fluoride and IIIb with aluminum chloride on the acid chloride yielded the same ketone, acid IIIb undoubtedly undergoing inversion of configuration during the cyclization. From the fact that the *cis* acid yielded the ketone under conditions which left the *trans* acid unchanged, and from the fact that the more stable configuration of the hydrindane ring system is known to be *cis*[9] the ketone is assigned the structure VIa. The *trans* isomer VIb may possibly be present in the product obtained from IIIb but it was not isolated.

Series B [Ring C Seven-membered (m = 2); Ring B Five-, Six-, and Seven-membered (n = 0, 1, 2)].—The 2-phenylcycloheptane-carboxylic (XV) -acetic (XII), and -propionic (XVII) acids required for cyclization to the series B ketones were prepared from 2-phenylcycloheptanone (IX) which was synthesized from cyclohexanone and phenyldiazomethane as previously described.[10] A Reformatsky reaction with 2-phenylcycloheptanone yielded a mixture of acids from which a small amount (7%) of 2-phenylcycloheptene-Δ^1-acetic acid (X) could be separated by crystallization. The position of the double bond in this compound was established through the ultraviolet absorption spectrum which showed a strong band (ϵ_{max} 7,800) at 243.5 mμ which is similar to the spectrum of 1-phenylcyclohexene[11] (ϵ_{max} of 6170 at 246 mμ) and different from the spectrum of crotonic acid[12] (ϵ_{max} of 100 at 250 mμ). Remaining after the separation of X was an oil, XI, presumed to be a mixture of X and 2-phenylcycloheptylideneacetic acid. Catalytic hydrogenation of X yielded a 2-phenylcycloheptaneacetic acid (XIIa), which could be purified by recrystallization. Hydrogenation of the residual mixture, XI, however, yielded a mixture of *cis*- and *trans*-2-phenylcycloheptaneacetic acids (XII) which could not be separated by crystallization. It was possible to separate the mixture into one of its pure components by a fractional crystallization of the S-benzylthiouronium salt, but unfortunately the acid so obtained was identical with the one produced by hydrogenation of X. By analogy to the findings of Linstead[13] acid XIIa has been assigned the *cis* configuration. Cyclization of XIIa with anhydrous hydrogen fluoride produced a liquid ketone (XIVa) while cyclization of XII under the same conditions yielded an oil from which a solid ketone (XIVb) was obtained. The assignment of configurations to these 6,6a,7,8,9,10,11,11a-octahydro-5-keto-5H-cyclohepta[*a*]naphthalenes is based on the following: (a) the observations given above regarding the probable *cis* configuration of XIIa; (b) the analogy to series A in which the *cis* acid IVa yielded a liquid ketone and the *trans* acid IVb yielded a solid ketone; (c) ultraviolet absorption data.

A Barbier–Wieland degradation of XII furnished 2-phenylcycloheptanecarboxylic acid (XV) as a mixture of *cis* and *trans* isomers which was not separated but was directly cyclized to 4b,5,6,7,8,-9,9a,10-octahydro-10-ketocyclohepta[*a*]indene (XIII). The pure ketone, obtained by purification through the semicarbazone, probably has the *cis* configuration by analogy to VIa of series A.

The conversion of XII to 2-phenylcycloheptanepropionic acid (XVII) by the Arndt–Eistert method proceeded with variable and often poor results until each step was separately investigated. The method of forming the acid chloride with thionyl chloride proved to be inapplicable due to the destruction of XII by this reagent. Phosphorus pentachloride, however, formed the acid chloride in excellent yield. The diazoketone resulting

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(5) Fujise, *Ber.*, **71**, 2461 (1938).

(6) Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936).

(7) Linstead, Whetstone and Levine, THIS JOURNAL, **64**, 2014 1942).

(8) *Cf.* Johnson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 116.

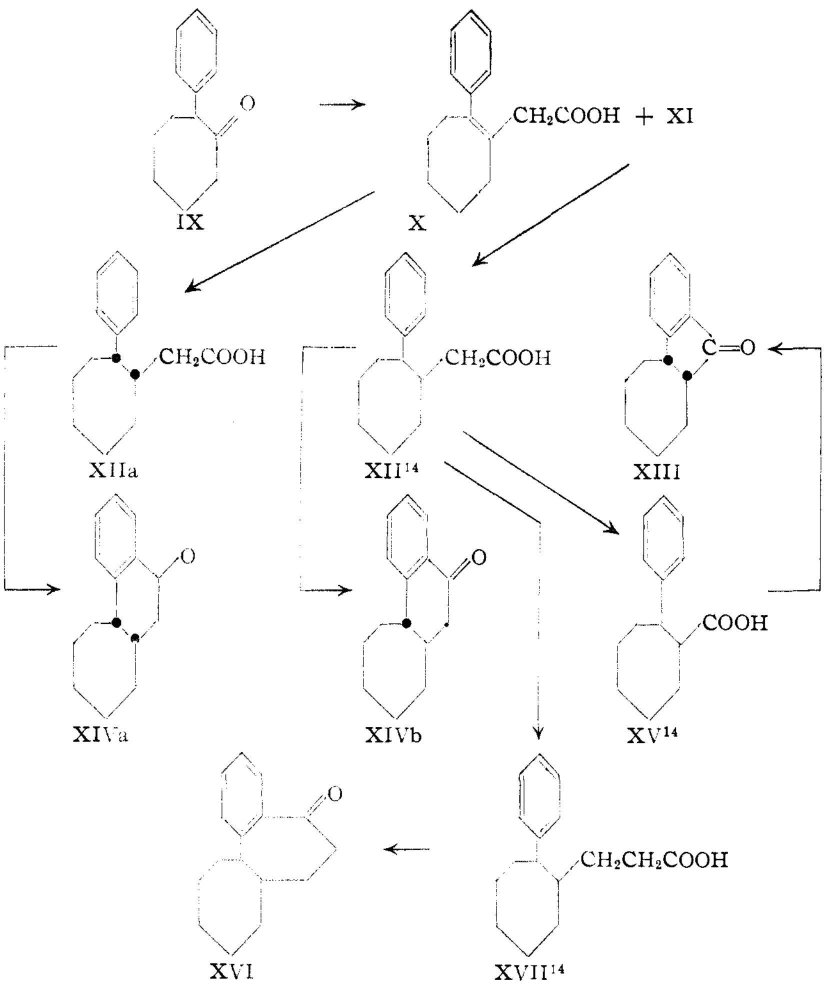
(9) Hückel and Friedrich, *Ann.*, **451**, 132 (1926); Hückel, Sachs, Yantschulewitsch and Nerdel, *ibid.*, **518**, 155 (1935).

(10) Gutsche, THIS JOURNAL, **71**, 3513 (1949).

(11) Pestemer and Wiligut, *Monatsh.*, **66**, 119 (1935).

(12) Mohler and Lohr, *Helv. Chim. Acta*, **21**, 485 (1938).

(13) Linstead, *et al.* (ref. 7), found that 2-phenylcyclohexene-Δ^1-acetic acid yielded 2-phenylcyclohexaneacetic acid almost exclusively in the *cis* form whereas 2-phenylcyclohexylideneacetic acid, under certain conditions of catalytic hydrogenation, yielded a mixture from which 57% of the *cis* isomer and 33% of the *trans* isomer were isolated.



from the action of diazomethane on the acid chloride of XII formed quite rapidly and gave the best results in the next step when used immediately. The Wolff rearrangement of the diazoketone to the ester of XVII gave capricious results when carried out in methanol in the presence of silver oxide. When effected by the recently described method of Wilds and Meader,[15] however, consistently good yields were obtained. A direct comparison of the two methods was made on the pure, solid diazoketone of IIIb. The methanol–silver oxide method gave IVb in 79% yield and in a rather impure state[16] whereas the high temperature benzyl alcohol–collidine method of Wilds and Meader produced IVb in a relatively pure state in 93% yield. A further difficulty was experienced in the isolation of XVII, for the sodium and potassium salts of this acid are soluble only in large volumes of water containing low concentrations of base. When all of these factors were taken into consideration fairly good yields of XVII were obtained from XII.

5,6,7,7a,8,9,10,11,12,12a-Decahydro-5-ketobenzo[*a*]heptalene (XVI) was obtained by two routes, both of which yielded the same stereochemical form of XVI. Cyclization of XVII yielded an oil from which a semicarbazone of m.p. 240° could be isolated by repeated recrystallization of the crude semicarbazone. Separation of XVII into one of its pure constituents by fractional crystallization of the S-benzylthiouronium salt followed by cyclization of the acid so obtained yielded a ketone from which the same semicarbazone (m.p. 240°) was easily obtained. An attempt to establish the configuration of XVI by relating XIIa to XVII and XVI was unsuccessful due to equivocal experimental data, and the difficult availability of XIIa prevented further work to this end. Unfortunately, comparisons of various infrared spectra provided no configurational evidence.

The ketone XVI is particularly interesting because the naturally occurring compound colchicine (I) is presumed to be a benzo[*a*]heptalene derivative.[17] The present synthesis of XVI represents the first time this new type of ring structure has been obtained by unequivocal methods and work is continuing in this Laboratory on the synthesis of other structures of this type.

Infrared Spectra.—The infrared spectra of the tricyclic ketones described above are shown in Fig. 1. All the spectra are similar in general character but close inspection reveals differences, particularly in the region between 6.6 and 12.0 μ. In the region from 2.0 to 6.6 μ the only significant difference is found in the carbonyl absorption band. In the five-membered ring ketones VIa and XIII the carbonyl bands are at 5.83 and 5.86 μ, respectively, appreciably displaced from the 5.93–5.95 μ position of the carbonyl bands in the six- and seven-membered ring ketones. This difference has been observed by Lecomte[18] in α-hydrindone, α-tetralone and α-benzsuberone. Lecomte also found a difference between the carbonyl bands in six- and seven-membered ring ketones which we, however, failed to detect. The C–H stretching vibration bands at 3.30, 3.46 and 3.54 μ and the phenyl ring band at 6.21 μ[19] showed little variation from one spectrum to another. In the 6.6 to 12.0 μ region appeared the most marked differences. Although it is not possible with the limited data so far available to associate the spec-

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[14] Acids XII, XV and XVII for which no stereochemical configurations are indicated are mixtures of the *cis* and *trans* isomers.

[15] Wilds and Meader, *J. Org. Chem.*, **13**, 763 (1948).

[16] We have previously (*cf.* ref. 2) reported an 84% yield of fairly pure IVb by this method.

[17] *Cf.* Loudon, *Ann. Rep.*, **45**, 190 (1948), for a review of the chemistry of colchicine.

[18] Lecomte, *J. Phys. Radium*, **6**, 257 (1945).

[19] Barnes, Gore, Stafford and Williams, *Anal. Chem.*, **20**, 402 (1948); Jones and Dobriner, "Vitamins and Hormones," Vol. VII, Academic Press, New York, N. Y., 1949, p. 293; Randall, Fuson, Fowler and Dangl, "Infrared Determination of Organic Structure," D. Van Nostrand Co., Inc., New York, N. Y., 1949.

tral pattern in this region with a specific type of ring structure it is hoped that comparisons in this region may serve as structure guides for other compounds in this series.

Ultraviolet Spectra.—The ultraviolet data are summarized in Table I. All of the ketones also possessed a strong absorption band near 200 mμ which, due to limitations of the spectrophotometer, could not be accurately measured. The most significant points to be noted are: (a) the shift of the position of the first absorption band to shorter wave length in the five-membered ring ketones, (b) the diminution of the extinction coefficients of the first absorption band in the seven-membered ring ketones, (c) the shift in position to shorter wave length of the second absorption band in *trans* ketones. The shapes of the curves showed no significant differences.

TABLE I

Compound	Size of ketone ring	First band λ_{max}, mμ	First band ϵ_{max}	Second band λ_{max}, mμ	Second band ϵ_{max}
VIa	Five-	245	11040	291	2180
XIII	Five-	245	10900	291	2220
VIIa	Six-	249.5	11580	294	1910
VIIb[a]	Six-	249.5	11780	292	1870
XIVa	Six-	249	11420	294	1860
XIVb	Six-	249	11100	292	1860
VIIIa	Seven-	249	7970	288	1460
VIIIb	Seven-	249	7700	286	1540
XVI	Seven-	248	7250	287	1300

[a] Mayneord and Roe, *Proc. Roy. Soc.* (London), **A158**, 634 (1937), found absorption maxima at 250 and 292 mμ for this compound.

Acknowledgment.—We wish to thank Mr. E. F. Binkerd and Dr. R. T. Rapala of Armour and Co., Chicago, Ill., for making the necessary arrangements for having the infrared spectra run and Mr. Arthur E. Brake, also of Armour and Co., for the actual measurements. We are indebted to Miss Dorothy Kuenne and Miss Patricia Clark for the microanalyses.

Experimental[20]

cis-**1,2,3,4,4a,9a-Hexahydro-9-ketofluorene (VIa) (a) From** *cis*-**2-Phenylcyclohexanecarboxylic Acid (IIIa).**—A 1.70-g. sample of IIIa (m.p. 74.5–76°) was treated for 2 hours with anhydrous hydrogen fluoride. The neutral product, 1.45 g. (93.5%) of a brown oil, was evaporatively distilled at 0.1 mm. to yield 1.25 g. (81%) of a very pale yellow oil which quickly solidified; m.p. 40–42°. Recrystallization from Skellysolve-A yielded colorless blades; m.p. 41.5–42.5° (reported 41.5–42°,[4] 43.5–44°[5]). The semicarbazone, formed in the usual manner with pyridine as the base, was obtained after several recrystallizations from ethanol as colorless needles; m.p. 212–213.5° (reported 212–213°,[4] 220°[21]).

(b) From *trans*-**2-Phenylcyclohexanecarboxylic Acid (IIIb).**—When 1.00 g. of IIIb was treated with anhydrous hydrogen fluoride for 3 hours only 0.05 g. of a neutral yellow oil was obtained, and 0.85 g. of the original IIIb was recovered. Conversion of IIIb to the acid chloride with thionyl chloride and treatment with anhydrous aluminum chloride according to previously described conditions[5] gave a 74% yield of a yellow oil; b.p. 125.5–126° (0.8 mm.) which slowly changed to a mushy, yellow solid. Several recrystallizations from Skellysolve-A produced long, very pale yellow blades melting at 42–43° and showing no depression in m.p. when admixed with the ketone obtained from IIIa.

cis-**1,2,3,4,4a,9,10,10a-Octahydro-9-ketophenanthrene (VIIa).**—A 4.00-g. sample of *cis*-2-phenylcyclohexaneacetic acid, IVa (m.p. 168–170°), after treatment for 5 hours with anhydrous hydrogen fluoride yielded 3.50 g. (95.5%) of a neutral, yellow oil. This was distilled through a semi-micro fractionating column[22] and a 2.0-g. fraction boiling at 130–131° (1.0 mm.) collected as a very pale yellow oil. Evaporative distillation under high vacuum did not remove any more of the color. The semicarbazone was obtained as colorless crystals; m.p. 194–195° (dec.) (reported 195–196°[4]).

trans-**1,2,3,4,4a,9,10,10a-Octahydro-9-ketophenanthrene (VIIb)** was obtained as previously described[23] by the anhydrous hydrogen fluoride cyclization of *trans*-2-phenylcyclohexaneacetic acid (IVb). The semicarbazone was obtained as colorless, glistening plates; m.p. 219–220° (dec.).

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44. Found: C, 69.86; H, 7.35.

cis-**6,7,7a,8,9,10,11,11a-Octahydro-5-keto-5H-dibenzo-[a,c]cycloheptatriene (VIIIa).**—A 1.5-g. sample of *cis*-2-phenylcyclohexanepropionic acid (Va) (m.p. 87–89°), was converted to the acid chloride by refluxing for 45 minutes with 1.5 g. of phosphorus pentachloride in 15 cc. of dry benzene. The cyclization of the acid chloride was patterned after a procedure described by Nunn and Rapson.[24] A solution of the acid chloride in 25 cc. of carbon disulfide was added over a period of 2 hours to a stirred suspension of 1.2 g. of anhydrous aluminum chloride in 80 cc. of carbon disulfide. The reaction mixture was then stirred and refluxed for 4 hours and worked up in the usual way to yield, after evaporative distillation at 0.001 mm., 1.28 g. (93%) of a yellow oil. Distillation of a 0.90-g. sample of this material through a semi-micro fractionating column[22] yielded 0.35 g. of a very pale yellow oil; b.p. 132–133° (0.1 mm.).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.99; H, 8.55.

The semicarbazone of VIIIa was obtained after several recrystallizations from ethanol as colorless needles; m.p. 236–238° (dec.).

Anal. Calcd. for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80. Found: C, 70.86; H, 7.79.

trans-**6,7,7a,8,9,10,11,11a-Octahydro-5-keto-5H-dibenzo[a,c]cycloheptatriene (VIIIb).**—A 1.90-g. sample of *trans*-2-phenylcyclohexanepropionic acid (Vb) (m.p. 81–83°) was converted to the acid chloride and cyclized as described above to yield 1.64 g. (94%) of a viscous, yellow oil which slowly solidified. Evaporative distillation followed by two recrystallizations from Skellysolve-A produced colorless, broad needles; m.p. 53–54°.

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.85; H, 8.23.

The semicarbazone of VIIIb was obtained as broad needles by recrystallization from methanol and as glistening plates by recrystallization from isopropyl alcohol or isobutyl alcohol; m.p. 274–276° (dec.).

Anal. Calcd. for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80. Found: C, 70.94; H, 7.83.

2-Phenylcycloheptene-Δ¹-acetic Acid (X).—The Reformatsky reaction was modeled after the one described by Cook and co-workers[6] for the preparation of 2-phenylcyclohexeneacetic acid. A 50.0-g. sample of 2-phenylcycloheptanone (prepared as described previously from phenyldiazomethane and cyclohexanone[10]) dissolved in 200 cc. of dry, thiophene-free benzene, was treated with 45 g. of ethyl bromoacetate and 17.5 g. of freshly activated[25] zinc. The stirred solution was heated until the reaction started and then allowed to reflux by itself for several minutes. External heating was then reapplied for 1 hour, in the middle of which time an additional 22 g. of ester and 8.7 g. of zinc were added. The hydroxy ester was isolated in the usual fashion and then dissolved in 100 cc. of dry ether and dehydrated with 20 cc. of purified[26] thionyl chloride and 53 cc. of dry pyridine. The unsaturated ester was isolated and distilled through an eight-inch Vigreux column to yield 51.5 g.

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[20] All melting points are corrected.

[21] Vocke, *Ann.*, **508**, 1 (1934).

[22] Gould, Holzman and Niemann, *Anal. Chem.*, **20**, 361 (1948).

[23] Gutsche and Johnson, THIS JOURNAL, **68**, 2239 (1946).

[24] Nunn and Rapson, *J. Chem. Soc.*, 1053 (1949).

[25] Fieser and Johnson, THIS JOURNAL, **62**, 575 (1940).

[26] Fieser, "Experiments in Organic Chemistry," 2nd. ed., D. C. Heath and Co., Boston, Mass., 1941, p. 381.

(75%) of a viscous, yellow oil; b.p. 140–168° (2 mm.). Saponification with aqueous alcoholic potassium hydroxide yielded 43.5 g. (71%) of a viscous, yellow oil which, when dissolved in Skellysolve-A and allowed to stand overnight in the ice-box deposited 4.25 g. (7%) of tan crystals; m.p. 104–107°. Two recrystallizations from Skellysolve-B yielded colorless, glistening needles; m.p. 115.5–117°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.40; H, 7.80.

The ultraviolet spectrum of X was measured[27] in 95% ethanol solution at 5×10^{-5} *M* concentration: $\lambda_{max.}$ 243.5 mμ, $\epsilon_{max.}$ 7800.

The mother liquor, after the separation of X, was evaporated and the residue, XI, treated as described in the following experiment, part b.

2-Phenylcycloheptaneacetic Acid (XII) (a) From 2-Phenylcycloheptene-Δ^1-acetic Acid (X).—A 4.25-g. sample of X, obtained as described above, was dissolved in ethyl acetate, treated with 1.0 g. of 10% palladium-on-charcoal catalyst (Baker Co.) and hydrogenated at room temperature and atmospheric pressure. After 75 minutes the theoretical amount of hydrogen for one double bond had been absorbed and the uptake ceased. The product was recrystallized from Skellysolve-A to yield 3.5 g. (82%) of colorless crystals; m.p. 88–90°. Two further recrystallizations yielded XIIa as colorless, short blades; m.p. 91–92°.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.67. Found: C, 77.30; H, 8.55.

The **S-benzylthiouronium salt of** ***cis*-2-phenylcycloheptaneacetic acid** was prepared according to the directions of Cheronis and Entrikin.[28] From 0.25 g. of the acid there was obtained 0.42 g. (98%) of a colorless powder; m.p. 153–154°. Recrystallization from ethyl acetate yielded colorless, feathery needles; m.p. 152.5–153°.

Anal. Calcd. for $C_{23}H_{30}N_2O_2S$: C, 69.30; H, 7.59. Found: C, 69.34; H, 7.45.

(b) From the Mixture XI.—A 38-g. sample of the liquid XI, obtained as described above, was dissolved in ethyl acetate and hydrogenated with a total of 10.0 g. of 10% palladium-on-charcoal as the catalyst. The hydrogen uptake was very slow and 24 hours was required for 95% absorption. The product consisted of 30.5 g. (79.5%) of a viscous oil which slowly changed to a colorless solid, XII; m.p. 47–65°. Recrystallization from Skellysolve-A afforded colorless crystals with m.p. 72–75° but further recrystallization did not raise the m.p. significantly. A 0.50-g. portion of this acid was converted to 0.84 g. (98%) of an S-benzylthiouronium salt; m.p. 141–144°. Upon repeated recrystallization of the salt, the m.p. gradually rose to 150–151° and this material showed no depression in m.p. when admixed with the S-benzylthiouronium salt of XIIa.

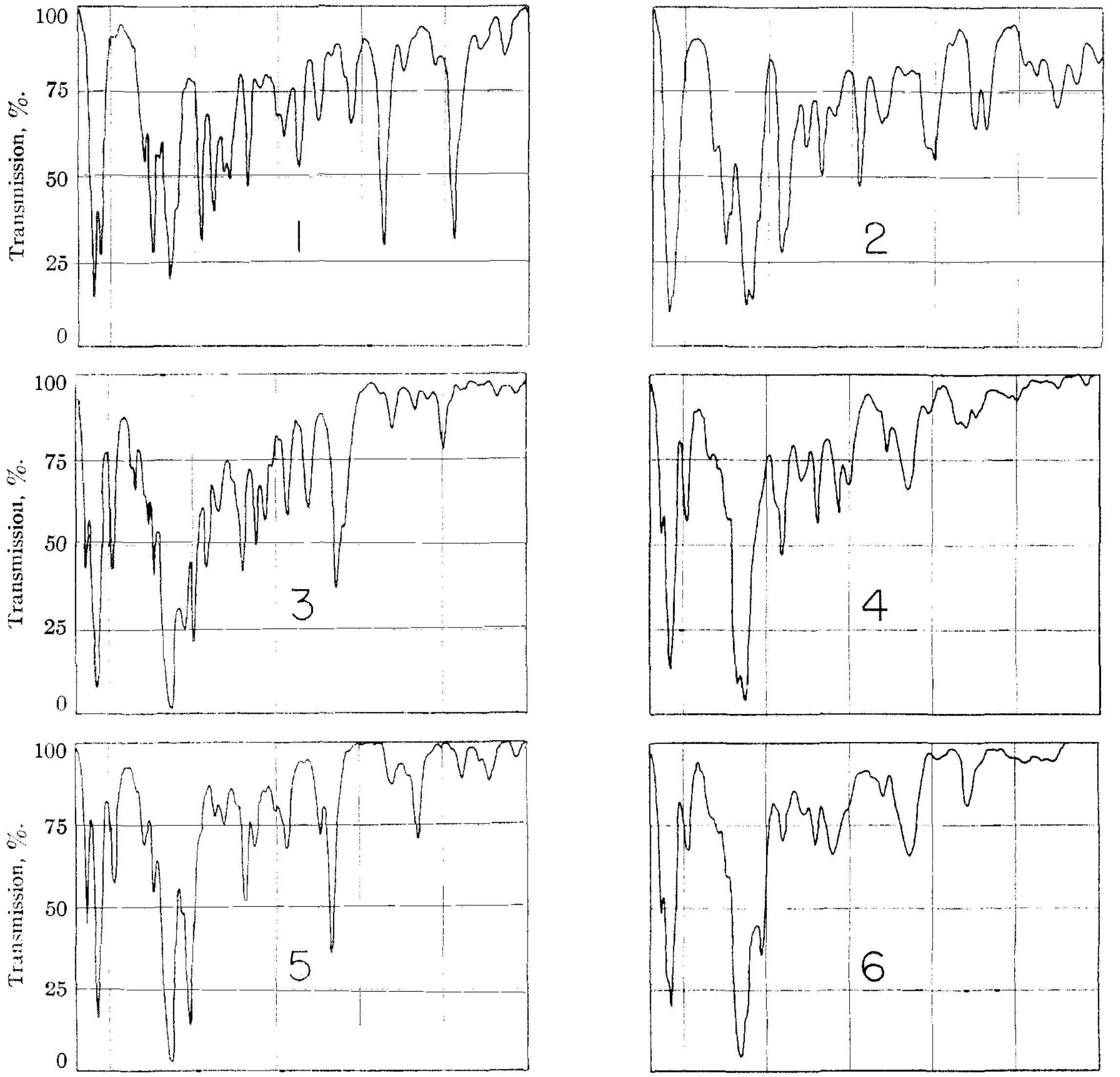

Fig. 1 (*continued on next page*).

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[27] We are indebted to Mr. K. L. Seligman for carrying out this measurement.

[28] Cheronis and Entrikin, "Semimicro Qualitative Organic Analysis," T. V. Crowell Co., New York, N. Y., 1947, p. 324.

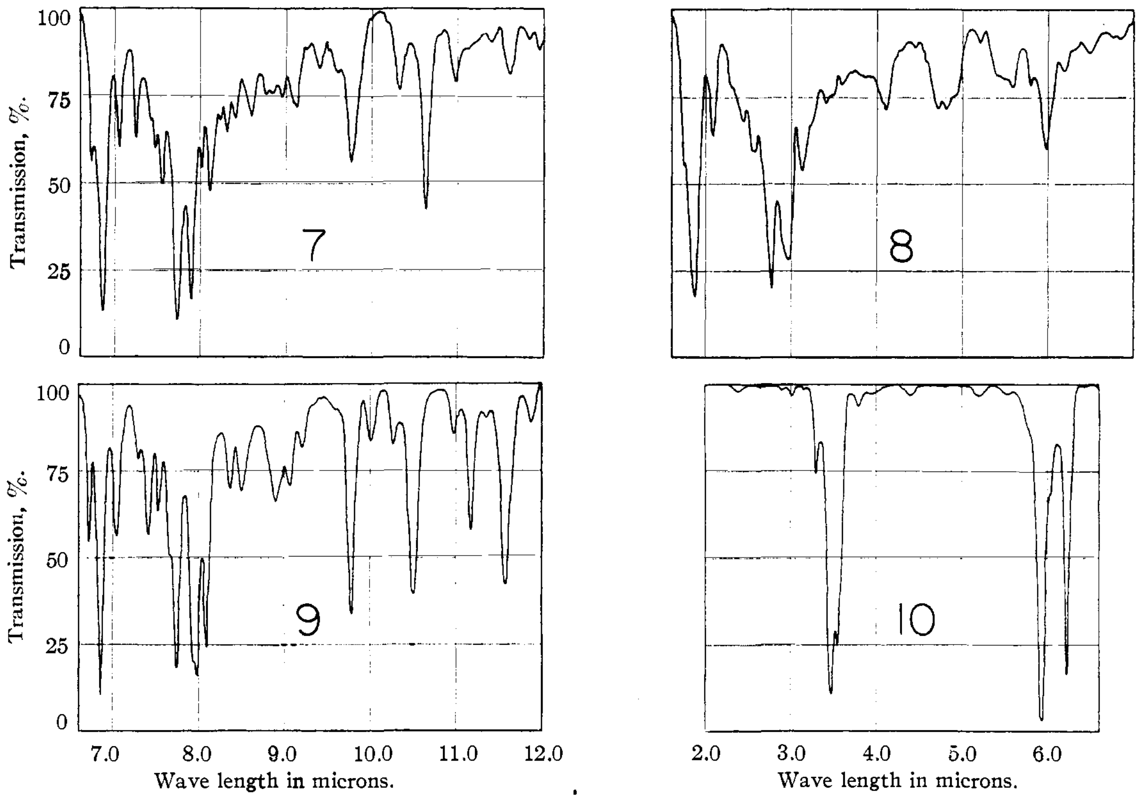

Fig. 1.—Infrared spectra: 1, VIa; 2, XIII; 3, VIIa; 4, XIVa; 5, VIIb; 6, XIVb; 7, VIIIa; 8, XVI; 9, VIIIb; 10, the 2.0–6.6 μ region which is the same for all of the above compounds except VIa and XIII in which the carbonyl band appears at 5.83 and 5.86 μ.

***cis*-6,6a,7,8,9,10,11,11a-Octahydro-5-keto-5H-cyclohepta[a]naphthalene (XIVa).**—A 3.5-g. sample of *cis*-2-phenylcycloheptaneacetic acid, XIIa (m.p. 89–91°), was treated with anhydrous hydrogen fluoride for 3 hours and the product isolated in the usual manner as 3.15 g. (97.5%) of a brown oil. Distillation through a semi-micro fractionating column[22] yielded a very pale yellow oil; m.p. 138–139° (0.5 mm.).

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.07; H, 8.19.

The semicarbazone of **XIVa** was obtained after two recrystallizations from ethanol as colorless, glistening plates; m.p. 201.5–202.5° (dec.).

Anal. Calcd. for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80. Found: C, 70.82; H, 8.06.

***trans*-6,6a,7,8,9,10,11,11a-Octahydro-5-keto-5H-cyclohepta[a]naphthalene (XIVb).**—A 16.6-g. sample of 2-phenylcycloheptaneacetic acid, XII (m.p. 47–65°), after treatment for 3 hours with anhydrous hydrogen fluoride yielded 14.9 g. (97.5%) of a brown oil. After standing for several days this changed to a mush from which a sticky solid was obtained by pressing the material on a porous plate. Recrystallization from Skellysolve-A yielded 3.50 g. of buff-colored crystals in the first crop, m.p. 36–37°, and 1.75 g. of brown, very sticky crystals in the second crop. Evaporative distillation of a portion of the first crop material at 0.2 mm. followed by two recrystallizations from Skellysolve-A yielded colorless plates; m.p. 60.5–61°.

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.26; H, 8.34.

The semicarbazone of XIVb was obtained as colorless, long blades after recrystallization from ethanol; m.p. 175.5–177.5° (dec.).

Anal. Calcd. for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80. Found: C, 70.61; H, 7.69.

4b,5,6,7,8,9,9a,10-Octahydro-10-ketocyclohepta[a]indene (XIII).—A 9.5-g. sample of XII (m.p. 47–65°) was subjected to a Barbier–Wieland degradation according to previously published conditions[29] to yield 4.0 g. (45%) of 2-phenylcycloheptanecarboxylic acid (XV). A 2.5-g. sample of this acid was converted to the acid chloride and treated with aluminum chloride as described above for the preparation of VIa. The product consisted of 1.90 g. (83%) of a yellow oil. A 1.25-g. portion of this was evaporatively distilled at 0.5 mm. and converted to the semicarbazone of XIII which, after three recrystallizations from ethanol, consisted of 0.45 g. of colorless crystals; m.p. 228–229.5° (dec.).

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44. Found: C, 69.41; H, 7.30.

A 0.39-g. portion of the semicarbazone was refluxed for several hours in an atmosphere of nitrogen with a 10% solution of aqueous oxalic acid to yield 0.20 g. (66%) of ketonic material. Evaporative distillation at 0.2 mm. yielded XIII as a pale yellow oil.

Anal. Calcd. for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.50; H, 7.75.

2-Phenylcycloheptanepropionic Acid (XVII) (a) Factors Influencing the Arndt–Eistert Reaction.—The inapplicability of thionyl chloride for the preparation of the acid chloride is illustrated by the following experiment: a 0.50-g. sample of XII (m.p. 47–65°) was refluxed for 4 hours with 3 cc. of purified[26] thionyl chloride; the residue after removal of the thionyl chloride was hydrolyzed with aqueous potassium hydroxide to yield 0.04 g. of base-soluble material and 0.44 g. of neutral, resinous, very high boiling material. The completeness of the formation of the diazoketone is illustrated by the following experiment: the acid chloride from a 0.33-g. sample of XII was converted to the diazoketone by treatment at 0° over a period of 10 minutes with ethereal diazomethane (from 2.5 g. of nitrosomethylurea); the reaction mixture was allowed to stand at 0° for 20 minutes longer, the ether was removed, and the residue was refluxed for 1 hour with aqueous alcoholic sodium hydroxide; the neutral fraction amounted to 0.27 g. and the base-soluble fraction to 0.04 g. A comparison of the Wolff rearrangement according to two different methods is given in the following experiment: a 0.75-g. sample of the diazoketone from IIIb (m.p. 100–102°) was treated as previously described[2] with silver oxide in methanol to yield 0.57 g. (79%) of IVb;

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[29] Lane and Wallis, THIS JOURNAL, 63, 1674 (1941).

m.p. 90–105°; a similar sample treated by the benzyl alcohol–collidine method[15] yielded 0.67 g. (93%) of IVb, m.p. 103–108°.

(b) **Typical Preparation of XVII.**—An 8.30-g. sample of XII (m.p. 47–65°) was converted to the acid chloride by refluxing for 45 minutes with 8.00 g. of phosphorus pentachloride in 40 cc. of benzene. The acid chloride was converted to the diazoketone by adding an ethereal solution of diazomethane (from 30 g. of nitrosomethylurea) to an ethereal solution of the acid chloride at 0° over a period of 10 minutes. The mixture was then allowed to stand at 0° for 20 minutes, and the ether was removed by evaporation under vacuum at or below room temperature. The residue was immediately dissolved in 40 cc. of benzyl alcohol and added, over a period of 10 minutes, to a mixture of 40 cc. of γ-collidine and 20 cc. of benzyl alcohol contained in a flask heated by an oil-bath at 190–200°. The hydrolysis and isolation were carried out as described[15] and 8.30 g. (94%) of a brown oil obtained. The product appeared to be contaminated with some non-acidic material, however, for an S-benzylthiouronium salt was formed in only 75% yield: a 0.67-g. portion of the product yielded 0.84 g. (75%) of the salt which, after repeated recrystallization from ethyl acetate, existed as colorless, very small plates; m.p. 145–146°.

Anal. Calcd. for $C_{24}H_{32}N_2O_2S$: C, 69.86; H, 7.82. Found: C, 69.76; H, 7.68.

5,6,7,7a,8,9,10,11,12,12a-Decahydro-5-ketobenzo[a]-heptalene (XVI) (a) From XVII *via* the Semicarbazone.—A 10.5-g. sample of crude XVII was converted to the acid chloride and cyclized with anhydrous aluminum chloride as described for the preparation of VIIIa to yield 10.0 g. (108%) of neutral material. Distillation through an eight-inch Vigreux column yielded 5.65 g. (58%) of a yellow oil; b.p. 160–180° (3 mm.). A 3.45-g. portion of this product yielded 2.65 g. (61.5%) of colorless semicarbazone; m.p. 227–228° with some previous softening and dec. Two recrystallizations from ethanol yielded 1.28 g. (30%) of colorless, glistening, very small plates; m.p. 235–236° (dec.). Several further recrystallizations raised the m.p. to 239–240° (dec.).

Anal. Calcd. for $C_{17}H_{23}N_3O$: C, 71.54; H, 8.12. Found: C, 71.48; H, 7.96.

An attempt to convert the semicarbazone to the ketone by treatment with acetic acid and sodium nitrite[30] gave a resinous very high boiling material instead of the desired ketone. Hydrolysis with aqueous oxalic acid, however, was successful. A 1.28-g. sample of the semicarbazone (m.p. 235–236°) was refluxed for 9 hours in an atmosphere of nitrogen with 25 cc. of 10% oxalic acid. From the cooled reaction mixture 0.50 g. of unchanged semicarbazone was removed by filtration and the filtrate worked up in the usual way to yield 0.63 g. (100% based on recovered semicarbazone) of a viscous, yellow oil which, after evaporative distillation at 0.15 mm., yielded 0.55 g. (88%) of a very pale yellow oil.

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.26; H, 8.57.

An attempt to improve the hydrolysis by carrying it out in aqueous alcoholic oxalic acid was not successful: a 0.30-g. sample of the semicarbazone refluxed for 6 hours with 1 g. of oxalic acid in 7 cc. of water and 7 cc. of ethanol yielded 0.20 g. of unchanged starting material.

(b) **From XVII *via* the S-Benzylthiouronium Salt.**—A 13.0-g. sample of the S-benzylthiouronium salt prepared from XVII was recrystallized three times from ethyl acetate to yield 3.40 g. of a salt with m.p. 141–142°. This material was shaken in benzene with dilute hydrochloric acid, water and 10% sodium hydroxide solution. The sodium hydroxide extract was washed with ether and then acidified to yield 1.86 g. of a yellow oil. This was converted to the acid chloride and cyclized to 1.45 g. (84.5%) of a brown oil. Evaporative distillation at 0.5 mm. yielded a pale yellow oil which formed a semicarbazone in 80% yield; m.p. 234.5–235.5° (dec.). Two recrystallizations from isopropyl alcohol yielded colorless, glistening plates; m.p. 239–240°, which showed no depression in m.p. when admixed with the semicarbazone described in part a.

Infrared Spectra.—The infrared spectra were taken on 10% solutions of the ketones in carbon tetrachloride in a Baird double beam recording spectrophotometer. The spectra over the region from 2.0 to 16.0 μ were measured, but due to the strong absorption of carbon tetrachloride between 12.0 and 14.0 μ bands in this area were obscured.

Ultraviolet Spectra.—The ultraviolet spectra were measured with a Beckman spectrophotometer on 5×10^{-5} M (first band) and 2.5×10^{-4} M (second band) solutions of the ketones in 95% ethanol.

Summary

Syntheses have been carried out and the stereochemical configurations established for *cis*-1,2,3,-4,4a,9a-hexahydro-9-ketofluorene, *cis*- and *trans*-1,2,3,4,4a,9,10,10a-octahydro-9-ketophenanthrene, *cis*- and *trans*-6,7,7a,8,9,10,11,11a-octahydro-5-keto-5H-dibenzo[a,c]cycloheptatriene, *cis*-4b,5,6,7,-8,9,9a,10-octahydro-10-ketocyclohepta[a]indene and *cis*- and *trans*-6,6a,7,8,9,10,11,11a-octahydro-5-keto-5H-cyclohepta[a]naphthalene. The synthesis has also been carried out but the stereochemical configuration not established for 5,6,7,7a,8,9,10,11,-12,12a-decahydro-5-ketobenzo[a]heptalene, a compound of particular interest because it possesses the ring structure presumed to be present in colchicine. The infrared and ultraviolet spectra of these tricyclic ketones have been determined and some correlations between the spectra, ring size, and stereochemical configuration have been established.

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[30] Goldschmidt and Veer, *Rec. trav. chim.*, **65**, 796 (1946).