105° (20 mm.), which contained[14] more than 95% of the *trans* isomer **13**. A pure sample of the **7-methyl-*trans*-perhydro-1-indanone** (**13**), collected from the gas chromatograph[14] had infrared absorption[15] at 1740 cm.$^{-1}$ with broad, partially resolved n.m.r. absorption in the region 7.5 to 9.0 τ including a doublet (J = 4 c.p.s.) centered at 8.86 τ (CH_3).

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

4,5,6,7-Tetrahydro-1-indanone (**8**).—3-Carbethoxy-3-(1-cyclohexenyl)propionic acid[22] was converted to the tetrahydroindanone **8** as previously described.[23] The product, obtained as a colorless liquid, b.p. 121–125° (15 mm.), n^{27}D 1.5200 [lit.[23] b.p. 83.5–85° (2 mm.), n^{18}D 1.5260], has infrared absorption[15] at 1700 cm.$^{-1}$ (cyclopentenone C=O) and at 1645 cm.$^{-1}$ (C=C), an ultraviolet maximum[16] at 237 mμ (ϵ 13,500) and complex n.m.r. absorption in the region 7.2 to 8.6 τ with no peak at lower field attributable to a vinyl proton.

A solution of 1.882 g. (13.8 mmoles) of the tetrahydroindanone **8** in 35 ml. of methanol was hydrogenated over 401 mg. of a 5% palladium-on-carbon catalyst at room temperature and atmospheric pressure. After the hydrogen uptake (330 ml. or 1.06 equiv.) ceased, the mixture was filtered, concentrated, and distilled to separate 1.6305 g. (85%) of *cis*-perhydro-1-indanone (**6**), b.p. 98° (16 mm.), which was identified with a subsequently described sample by comparison of retention times and infrared spectra.

7-Methyl-4,5,6,7-tetrahydro-1-indanone (**18**).—To a solution of 600 mg. (3.95 mmoles) of the *trans* ketone **13** in 10 ml. of ether, cooled to 0°, was added dropwise and with stirring, 650 mg. (4 mmoles) of bromine. The mixture was stirred for 10 min. and then concentrated and a solution of the residue in petroleum ether was washed with water and concentrated. A solution of the residual yellow oil (which darkened on standing) in 10 ml. of pyridine was refluxed under nitrogen for 8 hr. and then diluted with ether and filtered to separate the pyridine hydrobromide. The organic filtrate was washed successively with aqueous hydrochloric acid, water, aqueous sodium bicarbonate, and water and then dried and concentrated. Distillation of the residue in a short-path still afforded 348 mg. (59%) of a pale yellow oil which contained[14] the tetrahydroindanones **18** (85%) and **16** (15%). A sample of the tetrahydroindanone **16** was collected and identified with an authentic sample[6] by comparison of retention times and ultraviolet spectra. The pure tetrahydroindanone **18**, collected from the gas chromatograph, has infrared absorption[15] at 1700 cm.$^{-1}$ (cyclopentenone C=O) and at 1640 cm.$^{-1}$ (C=C), an ultraviolet maximum[16] at 238 mμ (ϵ 11,300) and complex n.m.r. absorption[15] in the region 7.3 to 8.7 τ (11 H, saturated C—H) as well as a doublet (J = 7 c.p.s.) centered at 8.95 τ (3 H, CH_3).

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

(22) This diester, b.p. 148–153° (0.47 mm.), n^{25}D 1.4921, was prepared as described by W. S. Johnson, C. E. Davis, R. H. Hunt, and G. Stork [*J. Am. Chem. Soc.*, **70**, 3021 (1948)], who report n^{25}D 1.4830, b.p. 150–155° (0.5 mm.).

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

Comparable mixtures of the tetrahydroindanones **16** and **18** were obtained by dehydrohalogenation of the crude bromo ketone thermally, with collidine or with lithium chloride and dimethylformamide. A solution of 424 mg. (2.82 mmoles) of the tetrahydroindanone **10** in 5 ml. of a 1 M solution of sulfuric acid in a benzene–acetic acid mixture (1:2 by volume) was heated to 125° in a sealed ampoule for 18 hr. After the mixture had been diluted with 50 ml. of petroleum ether and washed with aqueous sodium hydroxide, the organic layer was washed with water, dried, and concentrated. Distillation of the residue afforded 93 mg. (23%) of a liquid, b.p. 130–140° (20 mm.), which contained[14] 85% of the tetrahydroindanone **18**. A sample of the product was collected and identified with the previously described sample by comparison of retention times, infrared spectra, and ultraviolet spectra.

Perhydro-1-indanones 6 and 7.—A solution of 1.30 g. (9.56 mmoles) of the *trans* ketone **5** in 25 ml. of ether was hydrogenated over 150 mg. of a 30% palladium-on-carbon catalyst at room temperature and atmospheric pressure. After the hydrogen uptake ceased (260 ml. or 1.2 equiv.) the mixture was filtered, concentrated and distilled to separate 789.3 mg. (64%) of the *trans*-perhydroindanone **7**, b.p. 81.5–86.5° (10 mm.), n^{27}D 1.4764, containing[14] less than 9% of the *cis* isomer **6**. The product has infrared absorption[15] at 1740 cm.$^{-1}$ (cyclopentanone C=O), ultraviolet maxima[16] at 288 mμ (ϵ 29) and 237 mμ (ϵ 37, this latter peak is apparently attributable to contamination with a small amount of the unsaturated ketone **8**) and broad n.m.r. absorption[15] in the region 7.5 to 9.2 τ with no peaks attributable to vinyl hydrogen.

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

A solution of 400 mg. (2.95 mmoles) of the *cis* ketone **4** 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 ml. or 0.91 equiv.) ceased, the mixture was filtered and concentrated to leave 293 mg. (73%) of colorless liquid[24] containing 80% of the *cis* isomer **6** and 20% of the unsaturated ketone **8** (identified by comparison of the infrared spectra of a collected sample and the previously described material). The *cis* isomer **6**, collected from the gas chromatogram,[14] contained less than 11% of the *trans* isomer **7** and has infrared absorption[15] at 1740-cm.$^{-1}$ (cyclopentanone C=O), ultraviolet maxima[16] at 288 mμ (ϵ 22) and at 237 mμ (ϵ 71, apparently attributable to contamination with a small amount of the unsaturated ketone **8**), broad n.m.r. absorption[15] in the region 7.5 to 9.2 τ with no peaks attributable to vinyl hydrogen and a molecular weight (mass spectrum) of 138.

Equilibration Studies.—The positions of equilibrium listed in Table I were obtained by dissolving each of the *cis* and *trans* isomers in four times its volume of triethylamine. The solutions were sealed in ampoules and heated to 100°, samples being removed periodically for analysis.[14] For these analyses, the columns were calibrated by use of standard mixtures. The equilibrations were allowed to proceed until the values obtained with each *cis-trans* pair of isomers agreed to within 1%.

(24) The *cis* isomer **6** is reported to boil at 72–73° (6 mm.) with n^{25}D 1.4813. See ref. 23.

Perhydroindanone Derivatives. III. Acid-catalyzed Ring Closure[1,2]

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Received July 3, 1962

The preparation (Chart II) and cyclization (Chart I) of the lactone **2** to form the tetrahydroindanones **1**, **3**, and **4** are described.

The successful use of acid-catalyzed ring closures for the production of tetrahydroindanone[3] prompted us to consider this synthetic method for the preparation of appropriately substituted tetrahydroindanones. In particular our failure to obtain a satisfactory yield of the 7-methyltetrahydroindanone (**1**) by use of the Diels–Alder reaction and subsequent transformations,[2] led us to reinvestigate the reported[3a] conversion of the lactone

(1) Supported in part by National Science Foundation Grant No. G-9486 and in part by Petroleum Research Fund Grant No. 594 A.

(2) Part II, *J. Org. Chem.*, **28**, 31 (1963).

(3) For examples see (a) R. L. Frank and R. C. Pierle, *J. Am. Chem. Soc.*, **73**, 724 (1951); (b) S. Dev, *J. Indian Chem. Soc.*, **34**, 169 (1957); (c) S. Dev and C. Rai, *ibid.*, **34**, 266 (1957).

2 to the tetrahydroindanone **3**, since the reported[3a] isolation of only a single ketonic product **3** seemed ususual in a reaction which presumably involves carbonium ion intermediates and could lead to several products.

The results of this investigation, outlined in Chart I, confirmed this suspicion since three tetrahydroindanones **1**, **3**, and **4** were produced. Although this sequence provided us with an adequate sample of the desired tetrahydroindanone **1** for characterization, the yields obtained and the complexity of the reaction mixture excluded this approach for preparative purposes.

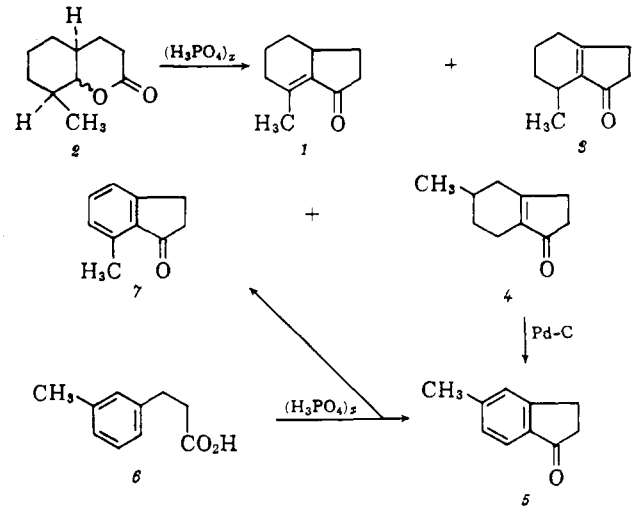


CHART I

Of incidental interest in this work was the finding that intramolecular cyclization of *m*-methylhydrocinnamic acid (**6**) does not yield a single product, 5-methylindanone (**5**), as previously reported,[4] but rather a mixture of both possible indanones **5** and **7**. Although the indanone **5** was formed in slightly larger amount, we suggest that any structure assignment based on the generalization[5] that intramolecular acylation will occur primarily *para* rather than *ortho* to a *meta*-substituent in the starting material should be made with caution.

The preparative routes employed for the lactone **2** and its isomers are outlined in Chart II. Although previous work had led us to expect only the keto acid derivative **9** from application of the Michael reaction to 2-methylcyclohexanone (**8**)[3a,6] and only the keto acid derivatives **11** and **12** by reaction of the enamine **10** with the methyl acylate,[7] the latter expectation was not realized, the ratio of product **9** to products **11** and **12** being approximately one to one. From the n.m.r. spectrum of the enamine mixture **10**, the ratio of the trisubstituted to the disubstituted enamine was estimated to be 15:85.[8] Consequently, the preference for attack at the unsubstituted position of a cyclohexanone enamine is no where near as great as had been supposed.[7,9] Of the two 2,6-disubstituted ketones **11a** and **12a** obtained from the quaternary salt **13**, the preponderant (and hence more stable) isomer has been

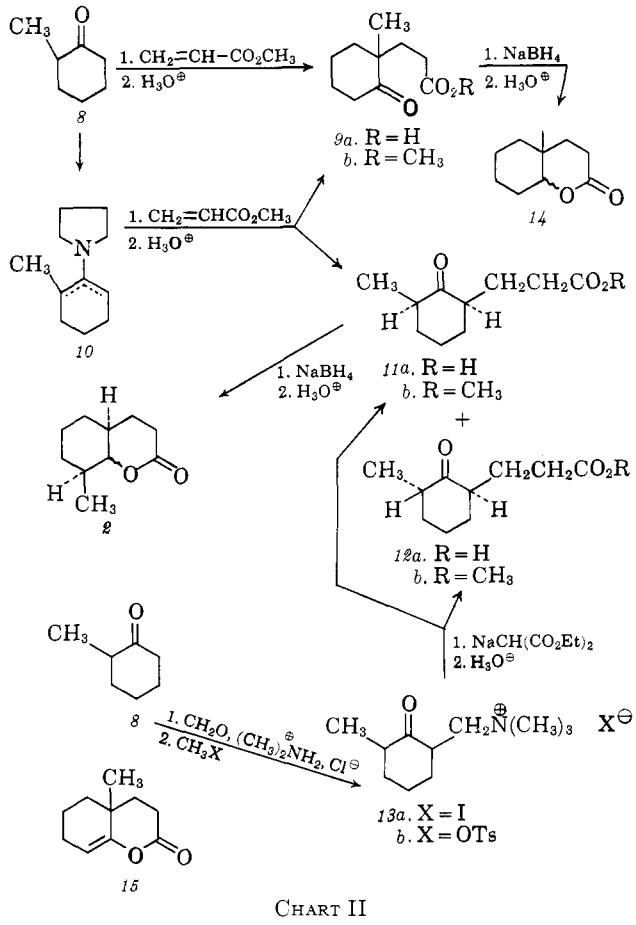


CHART II

assigned the *cis* configuration which is capable of existing in a conformation with both substituents equatorial. Reduction of each of the keto acids **9a** and **11a** yielded a mixture of stereoisomeric lactones.

Experimental[10]

β-(3-Methyl-2-oxocyclohexyl)propionic Acid Derivatives 11 and 12.—After 2-methylcyclohexanone[11] had been converted to 2-(dimethylaminomethyl)-6-methylcyclohexanone, b.p. 62–63° (0.7 mm.), n^{25}D 1.4639 [lit.[3a] 71° (1.3 mm.), n^{20}D 1.4650], as previously described,[3a] reaction of 45.9 g. (0.27 mole) of this Mannich base with excess (76.5 g. or 0.54 mole) of methyl iodide in 150 ml. of ether for 3 days afforded 71.2 g. (84.5%) of the crude methiodide **13a**. Extraction with methylene chloride removed the more soluble diastereoisomer **13a** which crystallized from a methylene chloride–ether mixture as white crystals, m.p. 160–163° dec. [lit.[3a] 163–164°], yield 28.2 g. (33.5%), infrared[12] 1705 cm.$^{-1}$ (C=O). The residue from the methylene chloride extraction consisted of 25.6 g. (30.5%) of the crude higher melting diastereoisomer **13a**, m.p. 190–192° dec., infrared[12] 1699 cm.$^{-1}$ (C=O). Alternatively, a solution of 78.8 g. (0.47 mole) of the Mannich base and 95.4 g. (0.51 mole) of methyl *p*-toluenesulfo-

(4) (a) J. von Braun, G. Manz, and E. Reinsch, *Ann.*, **468**, 277 (1929); (b) W. von Miller and Rohde, *Ber.*, **23**, 1887 (1890); see also Young, *Ber.*, **25**, 2102 (1892).

(5) W. S. Johnson, *Org. Reactions*, **2**, 114 (1944).

(6) (a) P. C. Dutta and N. R. Ghosh, *J. Indian Chem. Soc.*, **32**, 741 (1955). See also (b) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(7) G. Stork and H. K. Landesman, *ibid.*, **78**, 5128 (1956).

(8) *Cf.* G. A. Berchtold, unpublished work.

(9) In experiments to be described elsewhere the reaction of the enamine **10** with methyl *p*-toluenesulfonate was found to produce a mixture of quaternary ammonium salts which could be rearranged thermally and subsequently hydrolyzed to a mixture of 2-methylcyclohexanone and 2,6-dimethylcyclohexanone. *Cf.* G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

(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 ith 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 n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer.

(11) A. S. Hussey and R. H. Baker, *J. Org. Chem.*, **25**, 1434 (1960).

(12) Determined in chloroform solution.

nate in 350 ml. of ether was allowed to stand for 6 days. After filtration to remove 130 g. (78.5%) of the crude quaternary salt **13b**, the filtrate was concentrated and allowed to stand 4 weeks. The total yield of the crude quaternary salt **13b** obtained amounted to 160.5 g. (97%), m.p. 120–145°. Fractional crystallization of a portion of the material from methylene chloride–ether mixtures separated the pure lower melting diastereoisomer **13b** as white needles, m.p. 141–142°, infrared[12] 1705 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{18}H_{29}NSO_4$: C, 60.82; H, 8.22; N, 3.94; S, 9.00. Found: C, 60.88; H, 8.28; N, 3.83; S, 9.12.

A partially purified sample of the higher melting diastereoisomer **13b** was obtained as white prisms, m.p. 178–180°, infrared 1710 cm.$^{-1}$ (C=O) [Found: C, 59.30; H, 8.32; N, 3.66; S, 8.86]. Reaction of either the crude methiodide **13a** or the crude metho-*p*-toluenesulfonate **13b** with diethyl malonate and sodium ethoxide as previously described[3a] afforded mixtures of keto esters boiling within the range 78–142° (0.2–0.4 mm.), $n^{25}D$ 1.4519–1.4672, infrared[12] 1700–1740 cm.$^{-1}$ (broad, ester and ketone C=O). After a 25.70-g. fraction of the mixture had been hydrolyzed and decarboxylated by refluxing with 300 ml. of 20% aqueous hydrochloric acid for 21 hr., appropriate manipulations separated 15.83 g. of a mixture of propionic acids **11a** and **12a** as a viscous yellow oil. A solution of this crude acid mixture in an ether–petroleum ether mixture deposited 7.93 g. of the pure *cis* acid **11a** as white prisms, m.p. 72–73° [lit. 70°,[3a] 71°,[13] 73–74°[14]], infrared[15] 2600–3200 cm.$^{-1}$ (broad, carboxyl assoc. O—H), 1710 cm.$^{-1}$ (carboxyl and ketone C=O), ultraviolet[16] maximum 282 mμ (ε 25) with ε 86 at 210 mμ. After a 500-mg. sample (2.7 mmoles) of the crystalline *cis* keto acid **11a** had been treated with an excess of ethereal diazomethane, the ethereal solution was washed successively with aqueous sodium bicarbonate and aqueous sodium chloride, dried, and concentrated. Distillation of the residue in a short-path still afforded 410 mg. (76%) of the methyl ester **11b** as a colorless liquid, b.p. 70–80° (0.005 mm.), $n^{25}D$ 1.4604, infrared[15] 1737 cm.$^{-1}$ (ester C=O) and 1710 cm.$^{-1}$ (ketone C=O), ultraviolet[16] maximum 285 mμ (ε 23) with ε 98 at 210 mμ, n.m.r.[15] singlet at 6.42 τ (3*H*, O—CH_3) and doublet (J = 7 c.p.s.) centered at 9.04 τ (3*H*, CH_3—CH<) . The material exhibits a single peak on gas chromatography[17] and a single spot on thin-layer chromatography.[18]

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.86; H, 9.01.

An 825-mg. sample (4.5 moles) of the oily keto acid mixture **11a** and **12a** left after partial separation of the crystalline keto acid **11a** was esterified with diazomethane as previously described. The resulting ester mixture **11b** and **12b**, 711 mg. (80%), b.p. 70–80° (0.5 mm.), $n^{25}D$ 1.4601, was not resolved by gas chromatography[17] but was resolved by thin-layer chromatography indicating the presence of approximately equal amounts of **11b** and **12b**. This conclusion is substantiated by the subsequently described reduction of this mixture of keto acids **11a** and **12a** with sodium borohydride. The infrared spectrum[15] of this mixture was similar but not identical with the spectrum of the pure ester **11b**. Our efforts to obtain a pure sample of either the *trans* acid **12a** or the *trans* ester **12b** were unsuccessful.

β-(1-Methyl-2-oxocyclohexyl)propionic Acid Derivatives 9.—To a solution of 40.0 g. (0.356 mole) of 2-methylcyclohexanone and the potassium *t*-butoxide, prepared from 1.16 g. (0.0207 g.-atom) of potassium, in 300 ml. of *t*-butyl alcohol was added, dropwise and with stirring under nitrogen at room temperature, 25.6 g. (0.297 mole) of methyl acrylate. During the addition, which required 30 min. the reaction mixture was kept at 30° by the intermittent use of a cooling bath. The resulting mixture was stirred for 3 hr., diluted with 2 *N* aqueous sulfuric acid, and extracted with ether. The ethereal solution was washed with aqueous sodium chloride, dried, and concentrated. Distillation of the residue afforded 33.61 g. (57%) of the crude keto ester **9b** b.p. 99–107° (0.8 mm.), $n^{25}D$ 1.4805, which was shown by gas chromatography[17] to contain no appreciable quantity of the esters **11b** and **12b**. However, the thin-layer chromatogram[18] indicated the presence of an appreciable quantity of a second component and the infrared spectum[15] of this crude product, with absorption in the 6-μ region at 1755 cm.$^{-1}$ (shoulder, enol ester C=O), 1740 cm.$^{-1}$ (ester C=O), 1705 cm.$^{-1}$ (ketone C=O), and 1675 cm.$^{-1}$ (C=C), suggests that the contaminant is the enol lactone **15**. A 32.75-g. portion of this material was stirred with 400 ml. of refluxing 20% aqueous hydrochloric acid. After the resulting mixture had been concentrated under reduced pressure, saturated with ammonium sulfate, and extracted with ether, the acidic product was extracted from the ethereal solution with aqueous sodium bicarbonate and then recovered in the usual way. Distillation of the crude acid in a short-path still afforded 27.4 g. (90%) of the crude keto acid **9a** as a colorless liquid, b.p. 140° (0.1 mm.), which crystallized on standing, m.p. 40–45°. Recrystallization from ether–petroleum ether mixtures separated 20.8 g. (68.5%) of the pure keto acid **9a** as white plates, m.p. 46–48° [lit. 48°,[3a] 49–50°[6b]], infrared[15] 2600–3200 cm.$^{-1}$ (broad, carboxyl assoc. O—H), and 1710 cm.$^{-1}$ (carboxyl and ketone C=O). A 1.00-g. sample (5.4 mmoles) of this keto acid was treated with ethereal diazomethane as previously described to yield 960 mg. (89%) of the keto ester **9b** as a colorless liquid, b.p. 85–90° (0.2 mm.), $n^{25}D$ 1.4661, infrared[16] 1740 cm.$^{-1}$ (ester C=O) and 1705 cm.$^{-1}$ (ketone C=O), ultraviolet[16] maximum at 292 mμ, (ε 29) with ε 88 at 210 mμ, n.m.r. singlet at 6.42 τ (3*H*, OCH_3) and singlet at 8.98 τ (3*H*, CH_3—C—). The material exhibits a single gas chromatographic[17] peak and a single spot on thin layer chromatography.[18]

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.69; H, 9.25.

Samples (100 mg. or 0.5 mmole) of each of the esters **9b** and **11b** in solutions of potassium *t*-butoxide, prepared from 10 mg. (0.26 mg.-atom) of potassium and 10 ml. of *t*-butyl alcohol, were allowed to stand at room temperature for 3 hr. Neither of the recovered esters **9b** (70% recovery) or **11b** (63% recovery) contained[17,18] the other isomer, indicating that **9b** and **11b** are not interconverted under these conditions.

Reaction of the Enamine 10 with Methyl Acrylate.—The enamine **10**, prepared as previously described,[19] was obtained as a colorless liquid, b.p. 93–94° (2 mm.), $n^{25}D$ 1.5132 [lit.[19] b.p. 91–92° (5 mm.), $n^{20}D$ 1.5145]. The n.m.r. spectrum of the material (as a pure liquid) indicated the presence of 85% of the disubstituted isomer and 15% of the trisubstituted isomer as judged from integration of the triplet (J = 4 c.p.s.) centered at 5.79 τ (85% of 1*H* >C=CH—) and the doublet (J = 7 c.p.s.) centered at 8.93 τ (85% of 3*H*, CH_3—CH<). A singlet at 8.26 τ (CH_3—C=C—) is readily discernible but interference by other peaks prevents an accurate integration of this peak. A solution of 15.0 g. (0.091 mole) of the enamine **10** and 15.7 g. (0.182 mole) of methyl acrylate in 40 ml. of dioxane was refluxed under nitrogen for 66 hr. and then diluted with 8 ml. of water and refluxed for an additional 45 min. The resulting mixture was concentrated under reduced pressure and then diluted with ether and washed successively with dilute, aqueous hydrochloric acid, aqueous sodium bicarbonate, and aqueous sodium chloride. After the resulting ethereal solution had been dried and concentrated, distillation of the residue separated 11.86 g. (66%) of a mixture of keto esters as a colorless oil, b.p. 143–145° (10 mm.), $n^{25}D$ 1.4632, which contains[17] 49% of the keto ester **9b** and 51% of the keto ester **11b** (and presumably **12b**).[20] Each of these components was collected from the gas chromatograph[17] and identified both by retention times and by comparison of the infrared spectrum of the collected sample with the spectra of previously described samples.

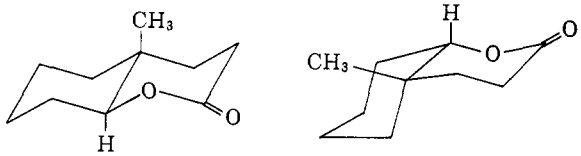
Reduction of the Keto Acid 9a.—To a solution of the sodium salt derived from 10.0 g. (0.0543 mole) of the keto acid **9a** in 100 ml. of water was added 765 mg. (20.2 mmoles) of sodium borohydride and the resulting solution was stirred for 19 hr. at room temperature. The resulting solution was acidified by the addition of excess hydrochloric acid and then stirred for 15 min., saturated with sodium chloride, and extracted with ether. After removal of the acidic components (0.64 g.) from the ethereal solution, the remaining ether solution was dried and concentrated. Distilla-

(13) N. N. Chatterjee and A. Bose, *J. Indian Chem. Soc.*, **18**, 196 (1941).
(14) H. Aebli and C. A. Grob, *Helv. Chim. Acta*, **40**, 2185 (1957).
(15) Determined in carbon tetrachloride solution.
(16) Determined in 95% ethanol solution.
(17) A column packed with Dow Corning silicone fluid no. 550 on ground firebrick was employed.
(18) A silica gel coating was employed.
(19) M. E. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959).
(20) Although the presence of small amounts of the *trans* keto ester **12b** in this mixture is very probable, we have no rigorous evidence establishing its presence since esters **11b** and **12b** were not resolved by the gas chromatography columns used and esters **9b** and **12b** were not resolved by thin-layer chromatography.

tion of the crude, neutral residue (8.26 g.) afforded 7.49 g. (82%) of a mixture of the *cis* and *trans* lactones **14** as a colorless liquid, b.p. 102–104° (0.8 mm.), $n^{25}D$ 1.4916, infrared[15] 1740 cm.$^{-1}$ (δ-lactone C=O), ultraviolet[16] absorption ε 65 at 210 mμ.

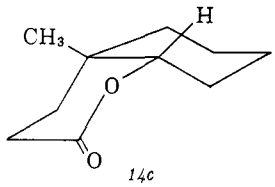
Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.40; H, 9.59.

The n.m.r. spectrum[15] of the material has a broad peak centered at approximately 4.0 τ (1*H*, >C(H)(O-)) and two peaks at 8.95 τ and 9.05 τ with a total area equivalent to three protons and relative areas of approximately 65% and 35%, respectively. The gas chromatograph of the lactone mixture exhibits two partially resolved peaks corresponding approximately to a 60%–40% mixture. Thus the n.m.r. peaks at 8.95 and 9.05 τ correspond to the grouping CH_3—C(—)— in the two diastereoisomeric lactones **14**. Since the change in n.m.r. absorption for the two isomers is found in the methyl peak and not in the peak attributable to the carbinol proton,[21] conformations **14a** and **14b**, both containing axial tertiary hydrogen atoms but containing, respectively, axial and equatorial methyl groups, become most probable for the *trans* and *cis* lactones **14**. Assuming that the correlation[22] derived for angular methyl groups in the decalin system will also be applicable to the lactones **14**, we have tentatively assigned the *cis* stereochemistry **14b** (or **14c**) to the lactone isomer comprising 60–65% of the lactone mixture. The n.m.r. peak attributable to the angular methyl group in this isomer (at 8.95 τ) is at 0.10 τ lower field than the corresponding peak in the other isomer.



14a

14b

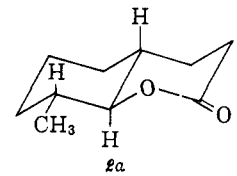


14c

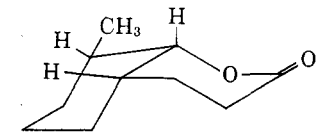
Reduction of the Keto Acid 11a.—A solution of the sodium salt derived from 7.50 g. (0.041 mole) of the keto acid **11a** and 580 mg. (0.0153 mole) of sodium borohydride in 75 ml. of water was stirred for 18 hr. at room temperature and then the mixture was worked up as previously described. The mixture of lactones **2** was collected as a colorless liquid, b.p. 87° (0.3 mm.), $n^{25}D$ 1.4855, yield 5.51 g. (80.5%). Redistillation through a 30-cm. Holtzman column gave an analytical sample, b.p. 110–111° (3 mm.), $n^{25}D$ 1.4825, infrared[15] 1735 cm.$^{-1}$ (δ-lactone C=O), ultraviolet[16] absorption ε 65 at 210 mμ.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39, H, 9.59. Found: C, 71.27; H, 9.58.

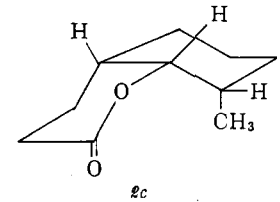
Although the gas chromatograph[17] of the product exhibits a single peak, the n.m.r. spectrum[15] is only consistent with the presence of both the *cis* (**2b**, **2c**) and *trans* (**2a**) lactones. Thus, in the region characteristic of the grouping >C(H)(O), are found a peak (half-band width 4 c.p.s.) at 5.80 τ and triplet ($J \sim 7$ c.p.s.) centered at 6.58 τ which together correspond in area to one proton. In addition two peaks (or more, splitting pattern not discernible), together attributable to the three protons of the methyl group, are found at 8.91 and 9.00 τ. The relative areas of the 5.80 peak–6.58 peak and the 8.91 peak–9.00 peak are 1 to 2. Of the two peaks attributable to the >C(H)(O) grouping, the broad peak at higher field (6.58 τ) may be safely assigned to the axial proton[21] in the *trans* isomer **2a** which is *trans* and coplanar to two adjacent C—H bonds.[22] Thus, the major product (60–70% of the lactone mixture) is the *trans* isomer **2a**.



2a



2b



2c

Reduction of a 728-mg. sample of the oily mixture of the keto acids **11a** and **12a** remaining after partial separation of the pure acid **11a** by the previously described procedure yielded 434 mg. of a lactone mixture, b.p. 50–60° (0.05 mm.), $n^{25}D$ 1.4870, which exhibits two gas chromatographic peaks corresponding to the lactones **2** (first peak eluted) and a second lactone component.

Acid-catalyzed cyclization of the Lactone 2.—To 12 g. of polyphosphoric acid heated to 78 ± 2° was added, dropwise and with stirring over a 15-min. period, 1.00 g. (5.9 mmoles) of the lactone **2**. After the addition was complete, the solution was stirred for 3 hr. at 78 ± 2° and then cooled and diluted with ice water. The resulting mixture was extracted with ether and the extract was washed successively with aqueous sodium bicarbonate and aqueous sodium chloride, dried, and concentrated. Distillation of the residue in a short-path still afforded 500 mg. of a pale yellow liquid, b.p. 60–80° (0.15 mm.), containing,[17] in order of elution, the tetrahydroindanones **1** (21%), **3** (22%), and **4** (27%) as well as the starting lactone **2** (30%). A collected sample of the unsaturated ketone **3** was shown to be identical with the previously described sample[23] by comparison of retention times and the infrared, ultraviolet, and mass spectra of the two samples. A solution of 400 mg. of the mixture in 15 ml. of ether was stirred with 3.5 ml. of 10% aqueous sodium hydroxide for 1 hr. to remove the lactone **2**. After the resulting ether solution had been washed with aqueous sodium chloride, dried, and concentrated, distillation of the residue afforded 210 mg. of a mixture of the ketones **1**, **3**, and **4**, b.p. 60–70° (0.15 mm.), from which larger samples of ketones **1** and **4** were collected.[17]

After collection and distillation, the ketone **1** was obtained as a colorless liquid with infrared peaks[15] of approximately equal intensity[24] at 1705 cm.$^{-1}$ (conj. C=O in a 5-membered ring) and 1640 cm.$^{-1}$ (conj. C=C) and ultraviolet maxima[16] at 256 mμ (ε (10,400) and 330 mμ (ε 98). The n.m.r. spectrum[25] (60 Mc.) has broad complex absorption in the region 7.5 to 8.5 τ but no peaks attributable either to a vinyl hydrogen atom or to a methyl group bonded to a saturated carbon atom.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39; mol. wt., 150. Found: C, 79.71; H, 9.57; mol. wt., 150 (mass spectrum).

Collection[17] and subsequent short-path distillation separated the ketone **4** as a colorless liquid with infrared absorption[15] at 1695 cm.$^{-1}$ (conj. C=O in a 5-membered ring) and 1640 cm.$^{-1}$ (conj. C=C, less intense than 1695 peak[24]) and an ultraviolet maximum at 237 mμ (ε 13,300). The n.m.r. spectrum[25] has a doublet (J = 6 c.p.s.) centered at 8.97 τ (3*H*, CH_3—CH<) and a peak at 7.58 τ (4*H*, CH_2 adjacent to C=O and CH_2 adjacent to C=C in 5-membered ring) but no peak attributable to a vinyl hydrogen atom.

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39; mol. wt., 150. Found: C, 79.59, H, 9.40; mol. wt., 150 (mass spectrum).

A mixture of 90 mg. (0.6 mmole) of the ketone **4**, 25 mg. of a 30% palladium-on-carbon catalyst, and 1 ml. of *p*-cymene was refluxed under nitrogen for 66 hr. and then filtered and chromatographed on 40 g. of Woelm activity II alumina. The indanone **5**, eluted with benzene–ether mixtures, amounted to 40.6 mg. (46.5%) of white crystals, m.p. 62–65°. Recrystallization from petroleum ether afforded 23 mg. (26%) of the pure indanone **5** as

(21) An equatorial proton of this type would be expected to occur at 0.5 to 0.8 p.p.m. lower field than an axial proton. For examples and leading references see E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, No. **3**, 97 (1962).

(22) J. I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961).

(23) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **28**, 31 (1963).

(24) The similar intensities of these two peaks is in accord with the presence of a *cisoid* α,β-unsaturated ketone system. R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).

(25) Determined as a solution in deuteriochloroform.

white needles, m.p. 69–70°, which was shown to be identical with the subsequently described material by a mixed melting-point determination and by comparison of infrared and ultraviolet spectra.

5-Methylindanone (5).—β-(*m*-Tolyl)propionic acid (**6**), m.p. 40.5–41.5° (lit.[4b] 42–43°), was prepared from *m*-bromotoluene *via* *m*-tolualdehyde[26] and *m*-methylcinnamic acid,[27] m.p. 115–116° (lit. 111.5°,[4b] 113–114°[27b]), as previously described. To 10 g. of polyphosphoric acid heated to 78 ± 2° was added, portionwise and with stirring over a 20-min. period, 718 mg. (4.36 mmoles) of the acid **6**. After the addition, the mixture was stirred at 78 ± 2° for 4.5 hr. and then cooled and diluted with ice water. The crude product, extracted with ether, was washed successively with aqueous sodium bicarbonate and aqueous sodium chloride, dried, and concentrated to leave 616 mg. (96.5%) of crude product as a yellow oil which crystallized on standing, m.p. 31–43°.[28] The thin-layer chromatogram[18] of the crude product indicated the presence of approximately equal amounts of two components, one of which has the same R_f value as 7-methylindanone (**7**). A 598-mg. sample of the crude product was chromatographed on 75 g. of silica gel to separate 272 mg. (43.5%) of crude 7-methylindanone (**7**) (eluted with 4:1 petroleum ether–ether), m.p. 51–53°, and 319 mg. (51.5%) of crude 5-methylindanone (**6**) (eluted with 1:1 petroleum ether–ether), m.p. 67–69°. Recrystallization from petroleum ether followed by sublimation afforded 144 mg. of pure 7-methylindanone (**7**) as white needles, m.p. 52.5–53.5°, identified with a previously described sample[23] by a mixed melting-point determination and comparison of infrared spectra.

Recrystallization from petroleum ether separated 229 mg. of the pure 5-methylindanone (**6**) as white needles, m.p. 69–70°, infrared absorption[15] at 1710 cm.$^{-1}$ (conj. C=O in a 5-membered ring), ultraviolet maxima[16] at 253 mμ (ε 15,500), 287 mμ (ε 3520), and 294 mμ (ε 3630). The sample has n.m.r. peaks[25] (60 Mc.) at 7.58 τ (3*H*, singlet, CH_3-), 7.2 to 7.5 τ (2*H*, multiplet) and 6.8 to 7.1 τ (2H multiplet), as well as peaks in the region 2.3 to 2.9 τ (3*H*, aromatic C–H).

Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.90; mol. wt., 146. Found: C, 82.37; H, 6.95; mol. wt., 146 (mass spectrum).

(26) L. I. Smith and M. Bayliss, *J. Org. Chem.*, **6**, 437 (1941).

(27) The Doebner modification of the Knoevenagel reaction was employed. (a) J. R. Johnson, *Org. Reactions*, **1**, 248 (1942); (b) P. N. Agarval, K. C. Pandya and I. L. Tripath, *Proc. Indian Acad. Sci.*, **22A**, 400 (1945).

(28) The supposedly pure 5-methylindanone previously prepared by this method (ref. 4) was reported to melt at 59–60°[4a] and at 59°.[4b]

Indole Alkaloids. I. Base-catalyzed Condensations with Yohimbanones and Alloyohimbanones[1]

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Received August 9, 1962

Base-catalyzed condensations of yohimban-17-one (**1**) with magnesium methyl carbonate, ethyl formate, and ethyl oxalate afforded 17-oxoyohimban-18-carboxylic acid (**2**), 18-hydroxymethyleneyohimban-17-one (**11**), and ethyl 17-oxoyohimban-18-glyoxylate (**24**), respectively. Esterification of β-keto acid **2** gave methyl 17-oxoyohimban-18α-carboxylate (**3**) [isomeric with yohimbinone (**6**)] which on reduction with sodium borohydride afforded 17α-hydroxy ester **4** and 17β-hydroxy ester **5**. Neither **4** nor **5** corresponded to yohimbine (**7**) or β-yohimbine (**8**), the known C-16 isomers. Treatment of 18-hydroxymethylene ketone **11** with hydroxylamine gave two isomeric isoxazoles **12** and **13**. On conversion with base of isoxazole **12** to 17-oxo-18α-carbonitrile **14** and reduction of **14** with sodium borohydride, 17α-hydroxynitrile **15** and 17β-hydroxynitrile **16** were obtained. Hydrolysis of **15** followed by esterification afforded 17α-hydroxy ester **4**. Similarly, **16** was converted to 17β-hydroxy ester **5**. Collidine treatment of the *O*-tosylate of 17α-hydroxy ester **4** gave α,β-unsaturated ester **18**, isomeric with apoyohimbine (**17**). These results show that carboxylation and formylation of yohimban-17-one occurred at the C-18 position. P.m.r. spectral measurements were used to confirm assignments of structure and configuration.

The chemistry of alkaloids of the β-carboline type has been studied extensively in recent years. Reserpine, one of the more complex members of this group, has been of special interest because of its stereochemical complexity and its pharmacological properties. Reserpine has substituents at positions 16, 17 and 18 in the E ring while most of the other structurally related alkaloids lack substituents at position 18. Since the C-18 trimethoxybenzoyloxy substituent of reserpine has an important influence on its pharmacological properties,[2] and since there is little known about C-18 substituted derivatives of yohimbine or its stereoisomers,[3] we became interested in a study of the introduction of activating groups, such as carboxyl and ethoxalyl, into several yohimbanes containing a keto group in the E ring. Such activating groups were considered an essential prerequisite for the selective introduction of other functional groups (*i.e.*, bromine, methyl, etc.) into the E ring.

A number of suitable E ring ketones have been prepared by transformations of known alkaloids[4] or by total synthesis.[5] However, few reactions have been reported in which these ketones have been utilized for the introduction of functional groups into the E ring. Russian workers have reported the introduction of ethoxycarbonyl[6] and formyl[7] groups at the C-16 position of yohimban-17-one (**1**); however, the reliability

(1) A portion of this work was presented at the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 3–8, 1961.

(2) R. A. Lucas, M. E. Kuehne, M. J. Ceglowski, R. L. Dziemian, and H. B. MacPhillamy, *J. Am. Chem. Soc.*, **81**, 1928 (1959); M. M. Robison, R. A. Lucas, H. B. MacPhillamy, W. Barrett, and A. J. Plummer, *Experientia*, **17**, 14 (1961).

(3) Oxygenation at the C-18 position of certain derivatives has been reported using microbiological techniques: S. C. Pan and F. L. Weisenborn, *J. Am. Chem. Soc.*, **80**, 4749 (1958); W. O. Godtfredsen, Y. Korsby, H. Loreck, and S. Vangedal, *Experientia*, **14**, 88 (1958).

(4) (a) B. Witkop, *Ann.*, **554**, 83 (1943); (b) J. Jost, *Helv. Chim. Acta*, **32**, 1297 (1949); (c) Z. J. Vjdělek and K. Macek, *Collection Czech. Chem. Commun.*, **24**, 2493 (1959); (d) A. Le Hir and E. W. Warnhoff, *Compt. rend.*, **246**, 1564 (1958); (e) S. Kimoto, M. Okamoto, and H. Kondo, *Chem. Pharm. Bull.* (Tokyo), **7**, 650 (1959); (f) A. Le Hir, M.-M. Janot, and R. Goutarel, *Bull. soc. chim.* France, 1027 (1953); (g) R. K. Hill and K. Muench, *J. Org. Chem.*, **22**, 1276 (1957); (h) E. Wenkert, E. W. Robb, and N. V. Bringi, *J. Am. Chem. Soc.*, **79**, 6570 (1957); (i) C. F. Huebner, A. F. St. André, E. Schlittler, and A. Uffer, *ibid.*, **77**, 5725 (1955); (j) R. C. Elderfield, A. E. Hydorn, E. Schenker, and K. K. Wyckoff, *J. Org. Chem.*, **24**, 1296 (1959).

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(6) L. A. Aksanova and N. A. Preobrazhenskiĭ, *Dokl. Akad. Nauk SSSR*, **117**, 81 (1957).

(7) G. S. Gusakova and N. A. Preobrazhenskiĭ, *ibid.*, **101**, 1061 (1955).