rolidino-5-methylcyclopent-2-en-1-one in 250 ml of dry ether. After the addition was complete, the mixture was refluxed for 0.5 hr. The Grignard complex was decomposed by putting it on ice and 15% hydrochloric acid. The mixture was allowed to stand overnight. The organic layer was separated and the water solution extracted with ether. The organic solutions were washed twice with small quantities of saturated salt solution. The ether was removed by distillation and the residue was refluxed with 200 ml of 25% sulfuric acid for 2 hr. The product was steam distilled leaving 1.5 g of residue. The distillate was extracted with ether after saturating with salt. After drying over magnesium sulfate, the solvent was removed by atmospheric distillation. There was produced 60.4 g (73%) of dihydrojasmone: bp 86–93° (2–3 mm); $n^{20}D$ 1.4788; λ_{max} 5.85 and 6.05 μ. The product was 99% pure as determined by vapor phase chromatography.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.33, 79.23; H, 10.49, 10.25.

A New Synthesis of (±)-Yohimbane

GLENN C. MORRISON, WIACZESLAW A. CETENKO, AND JOHN SHAVEL, JR.

Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey

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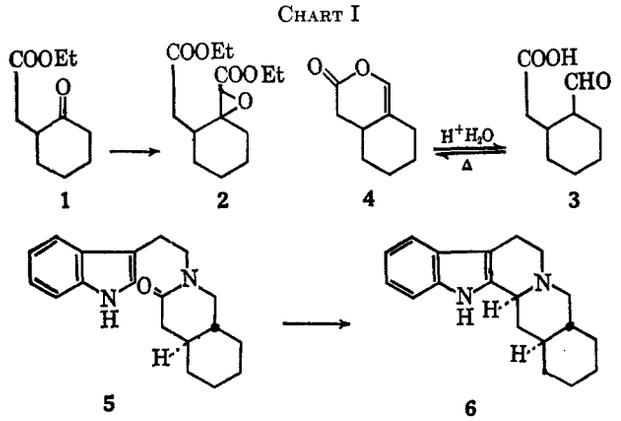
The total synthesis of (±)-yohimbane has already been reported by three groups, E. van Tamelen, *et al.*,[1] S. Corsano and L. Panizzi,[2] and J. Rubinfeld.[3] The goal of our work was not to design a synthesis as a proof of structure of (±)-yohimbane, but one which would lend itself to large-scale preparations of (±)-yohimbane.

For this purpose we have utilized the last two steps of the scheme of van Tamelen as did Rubinfeld.

CHART I



Therefore, more accurately, this paper describes a new preparation of *trans*-octahydro-2-[2-(indol-3-yl)ethyl]-3(2H)-isoquinolinone (**5**).

The ketone **1** was converted to the glycidic ester **2**, hydrolyzed, and decarboxylated to give the aldehyde **3** by a procedure analogous to that described by Johnson[4] for cyclohexanone. The crude acid aldehyde is a mixture of the *cis* and *trans* isomers of **3** and the anhydro actone **4** as shown by the infrared spectrum which shows absorption at 1720 cm^{-1} for the acid and aldehyde carbonyls and 1760 and 1660 cm^{-1} for the lactone carbonyl and double bond. The mixture was refluxed with dilute acid to hydrolyze the lactone and promote the establishment of an equilibrium mixture of the *cis* and *trans* isomers. Although the isomers were not isolated it was assumed that there was a large preponderance of *trans* since *trans*-1,2-dimethylcyclohexane is preferred over the *cis* isomer 20:1 on a thermodynamic basis.[5] Utilizing a procedure for the preparation of berberine derivatives,[6] the aldehyde **3** was condensed with tryptamine, reduced with potassium borohydride, and cyclized with acid to the lactam **5**. Since an authentic sample of **5** was not available for direct comparison we carried through the synthesis of (±)-yohimbane (**6**) which was shown to have an infrared spectrum[7] in chloroform identical with that of yohimbane derived from natural sources.

Since the previous workers in this field had not resolved (±)-yohimbane the unnatural isomer was still unknown. (+)-Yohimbane[8] was obtained from the racemic mixture by using (−)-dibenzoyltartaric acid as the resolving agent.

Experimental Section[9]

Ethyl 1,α-Epoxy-2-(ethoxycarbonylmethyl)cyclohexaneacetate (2).—To a mixture of 630 g of 2-(carboethoxymethyl)cyclohexanone and 420 g of ethyl chloroacetate was added a solution of 384 g of potassium *t*-butoxide in 3.2 l. of *t*-butyl alcohol over a 2-hr interval with cooling such that the temperature was maintained at 0–15°. After the addition had been completed stirring was continued for 2 hr at 0–15° and then 15 hr at room temperature. The solvent was removed *in vacuo* and the residue was treated with an ether–water mixture. The ether layer was washed with saturated sodium bicarbonate solution and water, dried over sodium sulfate, and the solvent was removed. Distillation of the residue gave 572 g (61%) of an oil: bp 128–130° (0.2 mm); $n^{25}D$ 1.4646; ν_{max}^{film} 1740, 1755 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.18; H, 8.11.

2-Formylcyclohexaneacetic Acid (3).—To a solution of 100 g of sodium in 1650 ml of ethanol which had been cooled to 10° was added 590 g of ethyl 1,α-epoxy-2-(ethoxycarbonylmethyl)cyclohexaneacetate. The mixture was cooled to 5° and 91.7 ml of water added dropwise with cooling such that the temperature remained at 0–15°. On standing at room temperature for 15 hr there was deposited 446 g of a crystalline solid, mp >330°. The salt was dissolved in 480 ml of water and 288 ml of hydrochloric acid was added with cooling such that the temperature remained at 10–15°. The solution was extracted with 3.0- and 1.0-l. portions of ether. The combined ether layers were washed with 100 ml of water and dried over sodium sulfate; the solvent was removed. The residue (340 g) and 10 g of copper powder was pyrolyzed at 250° (100 mm) for 5 hr. There was collected 185 g of a mixture, bp 50–192° (100 mm), which was refluxed vigorously with a solution of 73 ml of acetic acid in 1400 ml of water for 10 hr. The mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate and the solvent was removed. There remained 155 g (43%) of an oil.

A 1.0-g sample of the oil gave 0.65 g (48%) of the semicarbazone as a crystalline solid: mp 172–173.5° dec; ν_{max}^{Nujol} 1773, 1620,

(1) E. E. van Tamelen, M. Shamma, and P. Aldrich, *J. Am. Chem. Soc.*, **78**, 4628 (1956).

(2) S. Corsano and L. Panizzi, *Ann. Chim.* (Rome), **48**, 1025 (1958).

(3) J. Rubinfeld, Ph.D. Thesis, Columbia University, New York, N. Y., 1961.

(4) W. S. Johnson, J. S. Belew, L. J. Chinn, and R. H. Hunt, *J. Am. Chem. Soc.*, **75**, 4995 (1953).

(5) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 214.

(6) G. Muller and L. Vellu, German Patent 1,143,824 (1963).

(7) Supplied by H. Zinnes of this laboratory.

(8) J. Jost [*Helv. Chim. Acta*, **32**, 1297 (1949)] has reported (−)-yohimbane, mp 206°, $[\alpha]D$ −81° (*c* 0.50, alcohol).

(9) Melting points are corrected. The authors are indebted to Mr. A. Lewis and his associates, to Mr. R. Puchalski for the spectral data, and to Mrs. U. Zeek for analytical determinations.

1650, 1700, 2500, 3150, 3300, 3420 cm^{-1}; λ_{max}^{EtOH} 230 mμ (ε 13,800).

Anal. Calcd for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.54; N, 18.49. Found: C, 52.65; H, 7.78; N, 18.41.

***trans*-Octahydro-2-[2-(indol-3-yl)ethyl]-3-(2H)-isoquinolinone (5).**—To a solution of 155 g of 2-formylcyclohexaneacetic acid, 380 ml of triethylamine, and 560 ml of water in 700 ml of dimethylformamide was added a solution of 135 g of tryptamine and 350 ml of water in 430 ml of dimethylformamide at −5°. After the addition had been completed, the solution was stirred for an additional 30 min at the same temperature. Then 100 g of potassium borohydride was added over a 30-min interval, after which stirring at −5° was continued for 30 min. The cooling bath was removed and stirring was continued for an additional 75 min. The mixture was diluted with 940 ml of water, pH being adjusted to 6 with acetic acid, and was heated on the steam bath for 2 hr. On standing there was deposited a solid which after recrystallization from ethanol gave 156 g (57%) of a crystalline solid, mp 240.5–241°. Further recrystallization gave an analytical sample: mp 241.5–242° (lit.[1] 244–245°); ν_{max}^{Nujol} 747, 1627, 3230 cm^{-1}; $\nu_{max}^{CHCl_3}$ 1620, 3460 cm^{-1}; λ_{max}^{EtOH} 222 mμ (ε 37,300), 273 sh (ε 5700), 282 (ε 6200), 290 (ε 5400).

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.73; H, 8.16; N, 9.56.

(±)-Yohimbane (6).—A mixture of 102 g of *trans*-octahydro-2-[2-(indol-3-yl)ethyl]-3(2H)-isoquinolinone, 200 ml of phosphorus oxychloride, and 2 l. of benzene was refluxed for 4 hr. Filtration of the cold reaction mixture gave, after recrystallization from ethanol–dioxane, a yellow crystalline solid (88 g). This solid was dissolved in 750 ml of ethanol and 3 g of platinum oxide added; the mixture was hydrogenated at atmospheric pressure. Uptake ceased after absorption of the theoretical amount of hydrogen. The hydrogenation mixture was treated with 2 l. of chloroform and 2000 ml of 2% sodium hydroxide solution. The chloroform layer was washed with water and dried over sodium sulfate; the solvent was removed. The residue after recrystallization from ethanol gave 61 g (64%) of a crystalline solid, mp 179–180°. Further recrystallization gave an analytical sample: mp 182.5–183.5° (lit.[1] 181.5–183°); $\nu_{max}^{Nuj\ l}$ 740 and 3400 cm^{-1}; $\nu_{max}^{CHCl_3}$ 2850 and 2900 cm^{-1}; λ_{max}^{ETOH} 225 mμ (ε 32,000), 273 sh (ε 7500), 280 (ε 7900), 290 sh (ε 6700).

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.46; H, 8.76; N, 10.09.

(+)-Yohimbane.—A solution of 70.8 g of (±)-yohimbane and 91.5 g of O,O′-dibenzoyl-L-tartaric acid in 1.2 l. of ethanol was refluxed for 30 min. On standing there was deposited 92.0 g of a solid, mp 193–195°. Four recrystallizations from methanol gave 23.3 g of a solid, mp 178° dec. The salt was shaken with chloroform and 10% sodium hydroxide solution. The chloroform layer was washed with water and dried over sodium sulfate; the solvent was removed. Recrystallization of the residue from ethanol gave 10.0 g (28%) of a solid, mp 203–204°, $[\alpha]_D$ +81° (*c* 0.50, ethanol).[3]

Diiodocarbene and the Synthesis of Monoiodocyclopropane Derivatives[1]

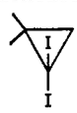
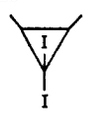
JOHN P. OLIVER AND U. V. RAO[2]

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Diiodocarbene was reportedly generated in the basic decomposition of iodoform[3] and appeared to add to cyclohexene[4] but the product was not fully characterized. Hine[5] pointed out that it would be of interest to establish the existence of this species and determine the stereochemistry of its addition to olefins because of its increased steric requirements and lower stability. For this reason and for use in our studies on the electronegativity effects of substituents on the proton coupling constants of trisubstituted cyclopropane derivatives,[6] it was found desirable to synthesize 1-iodo-2,2-dimethylcyclopropane *via* the carbene route. Hart[7] and Applequist[8] have synthesized iodocyclopropane derivatives by methods other than those involving carbene intermediates.

Reaction of isobutylene with iodoform in the presence of base gave rise to a high boiling fraction which could not be readily purified owing to its rapid decomposition. Evidence that this product contained 1,1-diiodo-2,2-dimethylcyclopropane (1) was obtained from its mass spectrum (see Table I) which indicated the presence of the molecular ion $C_5H_9I_2^+$. This in itself is sufficient to show the formation of the diiododerivative. However, the formation of the monoiodide, which can be more readily characterized, adds additional proof for the formation of the diiodide.

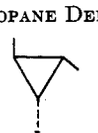
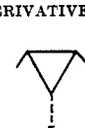
TABLE I
THE MASS SPECTRA OF ISOMERIC DIIODODIMETHYLCYCLOPROPANE DERIVATIVES

			
$C_5H_9I_2^+$	89.5[a]	44.6	96.6
$C_5H_9I^+$	98.3	100.0	100.0
$C_5H_8^+$	96.8	57.0	50.2
$C_5H_7^+$	100.0	96.8	94.6

[a] Relative abundances of the ions with an ionizing potential of 70 v.

The 1-iodo-2,2-dimethylcyclopropane (2) was obtained by reduction of (1) with tri-*n*-butyltinhydride[9] and was characterized by its infrared, nmr, and mass spectra and by chemical analysis. The infrared and nmr spectra were consistent with that of similar cyclopropane derivatives. The nmr spectrum of the ring protons analyzed as an ABC system gave $\delta_A = 6.758$, $\delta_B = 6.427$, and $\delta_C = 5.008$ ppm from the benzene with $J_{AB} = -5.64$, $J_{AC} = 4.85$, and $J_{BC} = 8.06$ cps. Details of this analysis will be given elsewhere.[6] Additional evidence was also obtained from its mass spec-

TABLE II
THE MASS SPECTRA OF ISOMERIC MONOIODOCYCLOPROPANE DERIVATIVES

				
$C_5H_9I^+$	5.7[a]	12.6	21.5	7.6
$C_5H_9^+$	95.2	85.0	81.5	114.5
$C_5H_5^+$	100.0	100.0	100.0	100.0

[a] The relative abundances of all ions have been adjusted to $C_3H_5^+ = 100$ and were obtained with a 70-v ionizing potential.

(1) Supported in part by the National Science Foundation Grant GP 3908.

(2) Taken in part from the Ph.D. Dissertation of U. V. Rao, submitted to Wayne State University, Detroit, Mich., 1965.

(3) J. Hine and S. J. Ehrenson, *J. Am. Chem. Soc.*, **80**, 824 (1958).

(4) W. Von E. Doering and A. K. Hoffmann, *ibid.*, **76**, 6162 (1954).

(5) J. Hine, "Divalent Carbon," the Ronald Press, New York, N. Y., 1964 p 46.

(6) U. V. Rao, M. T. Emerson, and J. P. Oliver, to be published.

(7) H. Hart and R. A. Cipriani, *J. Am. Chem. Soc.*, **84**, 3697 (1962).

(8) D. Applequist and D. F. O'Brien, *J. Am. Chem. Soc.*, **85**, 743 (1963).

(9) H. G. Kuivila and L. W. Menapace, *J. Org. Chem.*, **28**, 2165 (1963).