Studies in the Synthesis of Atisine. Terpenes. X

L. H. ZALKOW AND N. N. GIROTRA

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma

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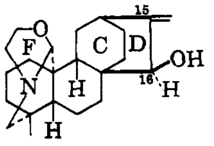
The carbon skeleton of atisine, a diterpenoid alkaloid, has been synthesized from maleopimaric acid. The latter compound has been prepared from abietic acid, which has been totally synthesized. The compound synthesized is enantiomeric with the isoprenoid portion of the naturally occurring alkaloid.

The synthesis of the diterpenoid alkaloid, atisine (I), has provided a challenge for many workers all over the world. During the past year approximately a dozen publications[1-11] have appeared dealing with various aspects of the synthesis of this interesting compound; Japanese workers[2] have recently reported the first total synthesis of the alkaloid in its racemic form.

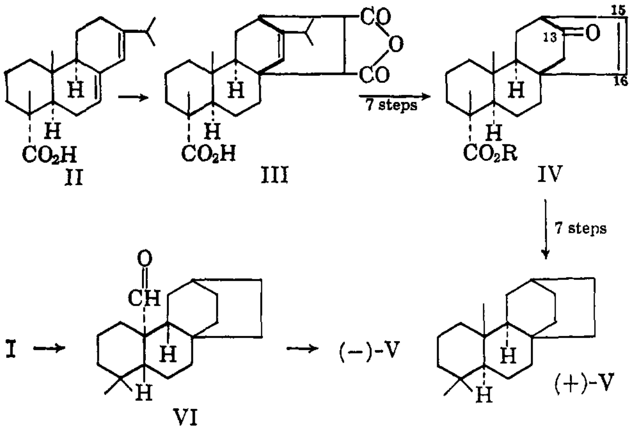


I

The problem involves two distinct phases. One, synthesis of the nitrogen-containing E ring and its subsequent conversion to the oxazolidine F ring, and second, construction of the C–D bicyclo[2.2.2]octane ring system with means of introducing the desired substituents at C-15 and C-16. A number of ingenuous methods have been utilized in the synthetic approaches to the nitrogen-containing E ring, involving classical reactions[2,10,11] and the more modern method of photolysis.[4,9] Likewise, a number of pathways have been offered for the synthesis of the bicyclic C–D ring system. Pelletier and Parthasarathy[5] used the Dieckmann reaction, Bell and Ireland[3] utilized an aldol type condensation, Nagata, *et al.*,[2] used a displacement reaction, and other workers[1,6] have approached the problem *via* the Diels–Alder reaction.

We have previously prepared[7] hydrocarbon (+)-V from maleopimaric acid (III) which in turn has been made by a Diels–Alder reaction between abietic acid (II) and maleic anhydride; abietic acid itself has been totally synthesized.[12,13] Ayer, McDonald, and Iverach[6] likewise synthesized (+)-V by a similar sequence of reactions and, in addition, found that it was, as predicted, enantiomeric with the product obtained by Wolf–Kishner reduction of VI, which had been previously obtained from atisine by Ap Simon, Edwards, and Howe.[14] We now wish to report the conversion of IV, an intermediate obtained in the preparation of V, into XXI, which possesses the entire diterpenoid skeleton of atisine in its correct relative configuration.

Reduction of keto ester IV with lithium aluminum hydride gave a mixture of alcohols (VIIa and b) which was oxidized directly to give the keto aldehyde VIII. Huang-Minlon[15,16] reduction of VIII gave crystalline alkene IX. The n.m.r. spectrum of IX showed the three methyl-group protons at C-4 and C-10 as sharp singlets at δ 0.82, 0.87, and 0.96. This is to be contrasted with compounds of this type which contain a double bond at C-13. In such cases the C-10 methyl-group protons appear at δ 0.50.[17] The vinylic protons in IX appeared as three sharp lines at δ 5.92, 5.95, and 6.02. The double bond in IX was hydrated by the Brown hydroboration procedure[18] to yield a mixture of alcohols XVI (a, b) and XVII (a, b) which was treated with chromic anhydride in pyridine. Chromatography of the oxidation product on alumina gave two ketones, A (m.p. 145–146°, λ_{max} 5.78 μ) and B (m.p. 146–148°, λ_{max} 5.81 μ) in a ratio of approximately 4:1, the less abundant isomer B being eluted first. That no skeletal rearrangement had occurred in these transformations was shown by the facile conversion of both ketones A and B to the previously reported hydrocarbon (+)-V by the Huang-Minlon[15,16] procedure. The n.m.r. spectra of ketones A and B were very similar except that in A the methylene protons adjacent to the carbonyl group gave a signal at δ 1.82, whereas in ketone B these protons appeared at δ 2.17. Ketone A gave a positive Cotton effect in its optical rotatory dispersion curve whereas ketone B showed a negative Cotton effect. Although the above information did not allow an unambiguous decision to be made as to



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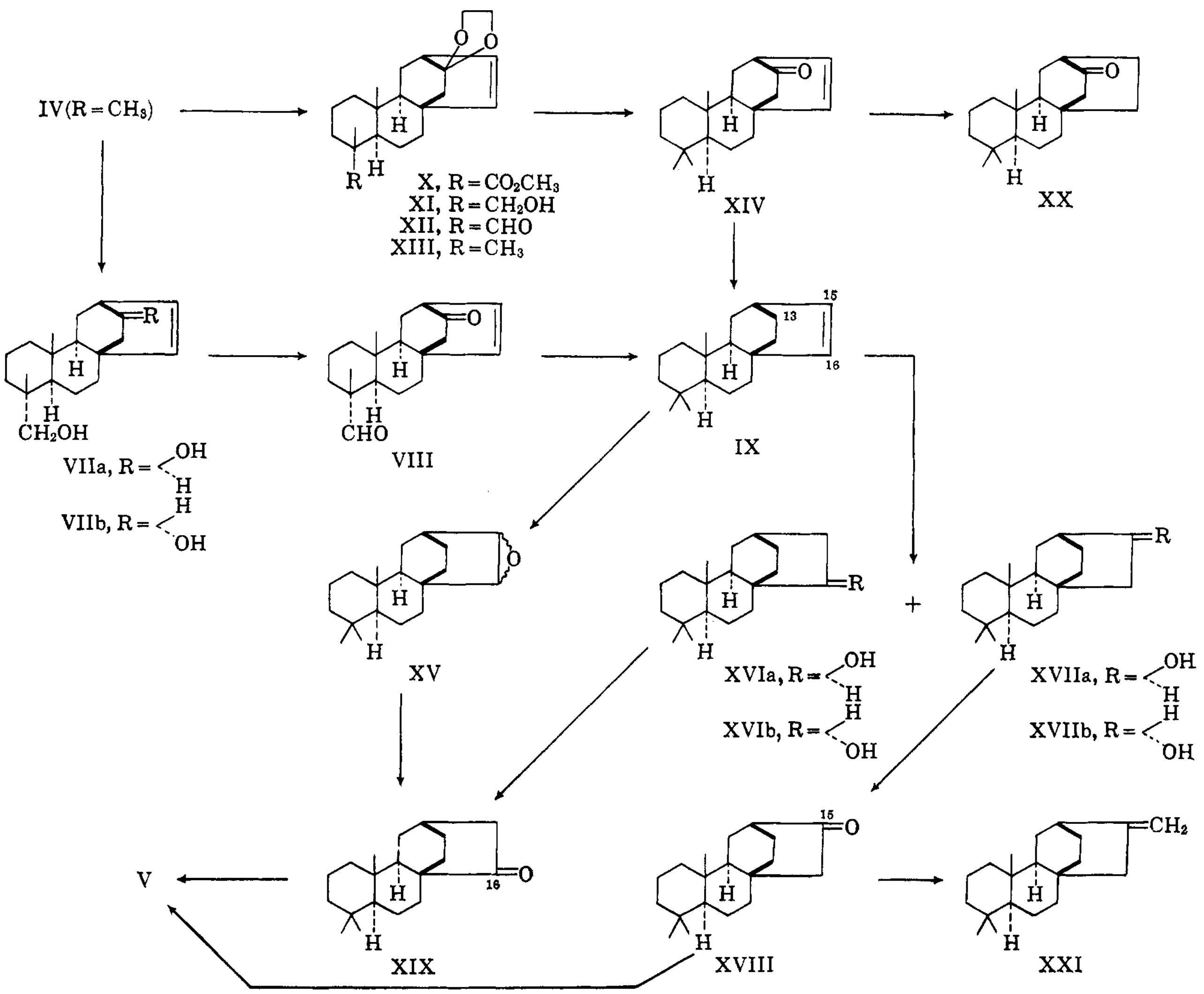
SCHEME I



the structures of isomers A and B, the ratio of products obtained in the hydroboration reaction and subsequent oxidation and the order of elution in chromatography indicated that A possessed the less hindered carbonyl group, *i.e.*, structure XVIII; therefore, B presumably had structure XIX. In order to obtain more information which would be useful in distinguishing between A and B, the isomeric ketone XX, of unequivocal structure, was prepared for comparison purposes.

Keto ester IV was converted to the cyclic ketal X by the usual procedure; the carbomethoxy group at C-4 was converted in turn to a hydroxymethyl group (XI) with lithium aluminum hydride, then to an aldehyde group (XII) by oxidation with chromic anhydride in pyridine, and finally to a methyl group (XIII) by the Huang-Minlon[15,16] procedure. Hydrolysis of the latter compound gave ketoalkene XIV, previously prepared by Ayer, *et al.*,[6] by a different procedure. Huang-Minlon[15,16] reduction of XIV gave the previously described alkene IX, while catalytic reduction of XIV gave the saturated ketone XX, which gave, as previously shown,[6] a positive Cotton effect in its optical rotatory dispersion curve. Unfortunately, it is not possible to use the Octant rule for predicting configuration in these cases since the C–D ring systems possess boat conformations.[19] Using an empirical approach, it can be seen that ketone XVIII possesses a mirror image relationship to ketone XX with regard to the C–D ring system and on this basis the unknown ketone with a negative Cotton effect (B) might be assigned structure XVIII. However, this turned out to be incorrect. During the course of this investigation Bell and Ireland[3] published their synthesis of racemic ketone XVIII by a path which placed the carbonyl function unequivocally at C-15. Comparison of the infrared and nuclear magnetic resonance spectra of racemic XVIII, kindly supplied by Dr. Ireland, with spectra of our ketone A showed that the two were identical, and hence ketones A and B possessed structures XVIII and XIX, respectively. Ketone (+)-XVIII was then converted to alkene XXI by use of the Wittig reagent,[20] thus completing the synthesis of the enantiomeric diterpenoid carbon skeleton of atisine. Bell and Ireland[3] likewise have reported the conversion of racemic XVIII to racemic XXI and succeeded in introducing a hydroxyl group at C-16 of XXI.

Alkene IX was readily converted into epoxide XV. However, when XV was treated with methylmagnesium iodide, the expected introduction of a methyl group at C-15 and/or C-16 did not occur. The product of the Grignard reaction gave, on oxidation with

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chromic anhydride in pyridine, the previously obtained ketone XIX. The unexpected preparation of the C-16 alcohol on treatment of epoxide XV with methylmagnesium iodide occurred either by direct reduction of the epoxide or by rearrangement of the epoxide to a C-16 ketone followed by reduction of the latter under the reaction conditions.

Experimental

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were recorded using a Beckman IR-5 spectrophotometer. Nuclear magnetic resonance spectra were recorded with the Varian A-60 n.m.r. spectrometer, using tetramethylsilane as an internal standard ($\delta = 0$) and carbon tetrachloride as solvent.

Preparation of VII.—A solution of IV (0.5 g.)[7] in 50 ml. of anhydrous ether was added dropwise to a well-stirred suspension of lithium aluminum hydride (0.16 g.) in 25 ml. of anhydrous ether. After the initial reaction was over, the mixture was refluxed for 3 hr. The excess hydride was decomposed by the successive addition of ethyl acetate and water, and the alkaline solution was made acidic with cold 6 *N* hydrochloric acid. The acidic solution was extracted with ether; the ether layer was washed with water, dried over anhydrous magnesium sulfate, and finally evaporated to yield 0.45 g. (m.p. 160–210°) of a mixture of VIIa and b; $\lambda_{\max}^{\text{KBr}}$ 2.98, 6.15, 9.38, 9.5, 9.6, 13.9, and 14.36 μ. This mixture was used in the next transformation without further purification.

Preparation of VIII.—A solution of 0.44 g. of VII (a, b) in 15 ml. of anhydrous pyridine was added to a mixture of 1.2 g. of chromic anhydride in 10 ml. of dry pyridine. After stirring for 2 hr. at room temperature, the mixture was poured into ice–water and extracted with ether. The ether extract was successively washed with 5% cold hydrochloric acid and 5% cold sodium hydroxide solution, and then dried over anhydrous sodium sulfate. Removal of the solvent gave 0.42 g. of the crude air-sensitive ketoaldehyde VIII, m.p. 112–118°; $\lambda_{\max}^{\text{KB}}$ 3.71, 6.18, 14.12, and 14.7 μ. This was used as such in the following reaction.

Preparation of IX from VIII.—Potassium hydroxide (5 g.) was heated with 5 ml. of 95% hydrazine and 45 ml. of diethylene glycol until it dissolved. The ketoaldehyde VIII (2.69 g.) was added to this solution and the reaction mixture was heated under reflux for 4 hr. Excess hydrazine and water were distilled out until the bath temperature reached 240°. The distillate was saved and the sublimed material was washed out of the condenser with ether. Hydrazine (5 ml.) was added to the residue; refluxing was continued for an additional 12 hr. The reaction mixture, distillate, and ether washings were combined and added to water (250 ml.); the entire mixture was extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of ether yielded 2.3 g. of the crude unsaturated hydrocarbon IX which on elution with petroleum ether (b.p. 60–80°) through 20 g. of neutral alumina yielded 2.04 g. of white crystalline solid, m.p. 82–83°. The analytical sample obtained by recrystallization from methanol had m.p. 84–85°; $\lambda_{\max}^{\text{KBr}}$ 6.19, 14.12, and 14.3 μ.

Anal. Calcd. for $C_{19}H_{30}$: C, 88.29; H, 11.70. Found: C, 88.16; H, 11.84.

Preparation of X.—A mixture of IV (3.81 g.), 20 ml. of anhydrous benzene, 2 ml. of freshly distilled ethylene glycol, and 0.03 g. of *p*-toluenesulfonic acid monohydrate was heated at reflux in a flask provided with a Dean–Stark water separator for 20 hr. The cooled mixture was poured into 5% sodium carbonate solution, and the organic layer was washed with water. Drying over anhydrous magnesium sulfate and evaporation of the solvent yielded 4.30 g. of viscous oil which crystallized on the addition of petroleum ether (b.p. 30–60°). Recrystallization from *n*-heptane yielded 4.14 g. (95.3%) of X, m.p. 95–97°. The analytical sample obtained by recrystallization from the same solvent had m.p. 98–99°; $\lambda_{\max}^{\text{KBr}}$ 5.8, 6.16, 8.0, 9.02, 9.15, and 14.5 μ; n.m.r. δ 1.03 (3 protons), 1.10 (3), 3.58 (3), 3.77 (4), and 5.85–5.94 (2).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.59; H, 8.94. Found: C, 73.88; H, 8.88.

Preparation of XI.—A solution of 3.8 g. of X in 40 ml. of anhydrous ether was added dropwise to a well-stirred suspension of 0.28 g. of lithium aluminum hydride in 25 ml. of anhydrous ether, and the reaction mixture was refluxed for 5 hr. The excess hydride was decomposed by the successive addition of ethyl acetate and water. After treatment with an excess of 20% aqueous ammonium chloride solution, the ether layer was separated and the aqueous layer was extracted with more ether. The combined ether layers were washed with water, then dried over anhydrous magnesium sulfate. Removal of the solvent yielded 3.49 g. of crude XI which upon crystallization from ether–petroleum ether gave 3.25 g. (92.8%) of material, m.p. 103–105°. The analytical sample was obtained by recrystallization from the same solvent and had m.p. 106–107°; $\lambda_{\max}^{\text{KBr}}$ 2.89, 6.17, 9.15, and 14.32 μ; n.m.r. δ 0.73 (3) 1.05 (3), 3.78 (4), and 5.85–5.94 (2).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.85; H, 9.72.

Preparation of XII.—A solution of 2.91 g. of XI in 15 ml. of anhydrous pyridine was added to a mixture of 4 g. of chromic anhydride and 30 ml. of anhydrous pyridine. After stirring at room temperature for 2 hr., the mixture was poured into ice–water and extracted with ether using Super Cel to break the emulsion. The organic layer was washed with water and dried over anhydrous magnesium sulfate; the solvent was evaporated to yield 2.84 g. of crude XII; $\lambda_{\max}^{\text{KBr}}$ 3.73, 5.8, 6.15, 9.15, and 14.25 μ. This was subjected to the following reaction without further purification.

Preparation of XIII.—A mixture of 2.76 g. of XII, 40 ml. of diethylene glycol, 6 ml. of 90% hydrazine, and 5 g. of potassium hydroxide was gently heated to dissolve the potassium hydroxide and then refluxed for 4 hr. Excess hydrazine and water were distilled at a bath temperature of 240°; 6 ml. of 90% hydrazine was again added; the reaction mixture was refluxed for an additional 16 hr. The cold mixture was diluted with 250 ml. of water and was extracted with ether. The organic layer was washed with water and, on drying over anhydrous magnesium sulfate followed by evaporation of the solvent, it yielded 2.38 g. of partially crystalline material which on crystallization from methanol yielded 1.4 g. of pure XIII, m.p. 90–90.5°; $\lambda_{\max}^{\text{KBr}}$ 6.15, 9.12, and 14.48 μ; n.m.r. δ 0.83 (3), 0.85 (3), 1.00 (3), 3.76 (4), and 5.85–5.94 (2).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.60; H, 10.54.

Preparation of XIV.—Concentrated hydrochloric acid (5 drops) was added to a solution of 1.2 g. of XIII in 15 ml. of methanol, 25 ml. of dioxane, and 5 ml. of water. The solution was stirred at room temperature for 1 hr. and then diluted with water (150 ml.). The aqueous layer was extracted with ether and the extract was washed successively with 5% sodium carbonate solution and water. Drying of the extract over anhydrous magnesium sulfate and evaporation of the solvent yielded 1.05 g. of a crystalline material which upon recrystallization from methanol gave 0.96 g. (93%) of pure XIV, m.p. 119–120°, lit.[6] m.p. 123–124°; $\lambda_{\max}^{\text{KBr}}$ 5.81, 6.82, and 14.15 μ; n.m.r. δ 0.83 (3), 0.93 (3), and 6.04–6.10 (2).

Anal. Calcd. for $C_{19}H_{26}O$: C, 83.76; H, 10.36. Found: C, 83.71; H, 10.47.

Preparation of IX from XIV.—A mixture of 10 ml. of diethylene glycol, 2 ml. of 95% hydrazine, and 2 g. of potassium hydroxide was heated until the potassium hydroxide dissolved. To the cooled mixture, 0.8 g. of the keto olefin XIV was added and the solution was refluxed for 28 hr. Water (250 ml.) was added to the cooled reaction mixture, and the solid that precipitated was extracted into ether. The ether extract was washed with water and then dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded a crystalline material which on recrystallization from methanol gave 0.6 g. (79%) of an olefin identical in all respects with IX, previously obtained as described above.

Preparation of XX.—A solution of 0.062 g. of XIV in 10 ml. of ethyl acetate was hydrogenated in the presence of 0.010 g. of 10% palladium–charcoal catalyst. The theoretical amount of hydrogen was absorbed within 10 min. The solid product (XX) obtained after the removal of the catalyst and evaporation of the solvent was crystallized from methanol, yielding 0.055 g., m.p. 125–126°, lit.[6] m.p. 126–127°; $\lambda_{\max}^{\text{KBr}}$ 5.81 μ; n.m.r. δ 0.80 (3) and 0.87 (3); optical rotatory dispersion run in methanol (*c* 0.055), $[\alpha]_{589\,\text{m}\mu}$ +40°, $[\alpha]_{310}$ +649°, and $[\alpha]_{295}$ +231°.

Preparation of XV.—An ethereal solution of monoperphthalic acid (9 ml., 4 mmoles) was added to a solution of 0.92 g. (~3.5 mmoles) of IX in 7 ml. of ether, and the mixture was allowed to stand for 48 hr. at room temperature. After that interval, 25 ml. of ether was added to the reaction mixture and excess peracid was destroyed by washing the ether layer with an aqueous solution of potassium iodide. The organic layer then was washed, respectively, with sodium thiosulfate, sodium carbonate solution, and water. The ether layer was dried over anhydrous magnesium sulfate and evaporation of the solvent yielded 0.96 g. of the crude epoxide XV, $\lambda_{\max}^{\text{KBr}}$ 11.49 μ. Crystallization from acetone gave 0.42 g. of epoxide which melted over a broad range, 70–112°; n.m.r. δ 0.80 (3), 0.87 (3), 0.95 (3), 2.55 (doublet, J = 5 c.p.s.), and 3.02 (triplet, J = 5 c.p.s.).

Conversion of XV to XIX.—XV (0.52 g.) in 15 ml. of anhydrous ether was added dropwise to an ethereal solution of methylmagnesium iodide (prepared by action of 0.15 ml. of methyl iodide in 5 ml. of dry ether on 0.05 g. of magnesium suspended in 2 ml. of anhydrous ether). The reaction mixture was refluxed for 42 hr., after an initial stirring at room temperature for 2 hr. The complex was hydrolyzed by means of 20% aqueous ammonium chloride solution. The clear ether layer was combined with ether extracts of the aqueous layer and washed with water. The organic layer was dried over anhydrous magnesium sulfate and evaporation of the solvent yielded 0.54 g. of a semicrystalline alcoholic product, $\lambda_{\max}^{\text{Nujol}}$ 2.98 and 9.58 μ. This product was oxidized without further purification.

A solution containing 0.52 g. of the above alcohol in 7 ml. of dry pyridine was added to a mixture of 0.7 g. of chromic anhydride and 6 ml. of dry pyridine, and the reaction mixture was stirred for 8 hr. at room temperature. The mixture was then poured into ice–water and extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 0.49 g. of partially crystalline solid ($\lambda_{\max}^{\text{film}}$ 5.81 μ) which was suspended in 60 ml. of methanol and 15 ml. of 15% aqueous sodium hydroxide solution, and the resulting mixture was heated at reflux for 8 hr. The cold mixture was diluted with 150 ml. of water and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate and evaporation of the solvent yielded 0.34 g. of yellow semicrystalline solid ($\lambda_{\max}^{\text{film}}$ 5.81 μ) which was chromatographed over 40 g. of neutral alumina. Elution with 50 ml. of 8.5:1.5 benzene–ether gave 0.114 g. of a ketone (m.p. 144–146°) which after recrystallization from methanol had m.p. 146–148°. This ketone was found to be identical in all respects with XIX prepared as described below.

Preparation of XVI and XVII.—To a well-stirred suspension of 0.21 g. of sodium borohydride in 20 ml. of anhydrous tetrahydrofuran containing 2.2 g. of IX, there was added 1 g. of boron trifluoride etherate in 8 ml. of anhydrous tetrahydrofuran over a period of 1 hr. at room temperature. After stirring for an additional 2 hr. at room temperature, the reaction mixture was heated under reflux for 1 hr. To the cold mixture 4 ml. of 3 N sodium hydroxide followed by 4 ml. of 30% hydrogen peroxide was added slowly. After 1.5 hr. 50 ml. of ether was added to the reaction mixture; the organic layer was separated and washed with water. The ether layer was dried over anhydrous magnesium sulfate and evaporation of the solvent yielded 2.38 g. of a mixture of alcohols XVI and XVII; $\lambda_{\max}^{\text{KBr}}$ 2.98, 9.4, and 9.52 μ.

Preparation of XVIII and XIX.—A solution of 2.37 g. of the above alcohol mixture in 30 ml. of anhydrous pyridine was added to a mixture of 3 g. of chromic anhydride and 30 ml. of anhydrous pyridine. The reaction mixture was stirred for 14 hr. at room temperature after which it was poured into ice–water. The aqueous solution was extracted with ether, the extract was washed, respectively, with 5% cold hydrochloric acid and 5% cold sodium hydroxide solution. The organic layer was dried over anhydrous magnesium sulfate and removal of the solvent yielded 2.27 g. of crude ketonic product. Chromatography of the mixture of ketones on alumina and elution with petroleum ether–benzene gave first 0.44 g. of pure XIX (m.p. 146–148°; $\lambda_{\max}^{\text{KBr}}$ 5.81 μ; n.m.r. δ 0.85 (3), 0.88 (3), 1.07 (3), and 2.17), then 0.422 g. of a mixture of XVIII and XIX, and finally 1.12 g. of pure XVIII, (m.p. 145–146°; $\lambda_{\max}^{\text{KBr}}$ 5.78 μ; n.m.r. δ 0.85 (3), 0.88 (3), 1.02 (3), and 1.82).

Ketone XIX had the following optical rotatory dispersion curve in methanol (c 0.051): $[\alpha]_{589\,\text{m}\mu}$ +19.6, $[\alpha]_{342}$ 0°, $[\alpha]_{310}$ −1242°, and $[\alpha]_{300}$ −776°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.01. Found: C, 83.18; H, 11.20.

Ketone XVIII had the following optical rotatory dispersion curve in methanol (c 0.051): $[\alpha]_{589\,\text{m}\mu}$ +183.2°, $[\alpha]_{308}$ +1145°, and $[\alpha]_{290}$ +760°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.01. Found: C, 82.48; H, 11.16.

Both ketone XVIII and XIX on Huang-Minlon[15,16] reduction gave hydrocarbon V identical in all respects with that previously reported.[17]

Preparation of XXI.—Methyltriphenylphosphonium bromide, 0.6 g. (prepared from methyl bromide and triphenylphosphine),[20] was added to an ethereal solution of n-butyllithium (obtained by addition of 0.21 g. of n-butyl bromide in 5 ml. of anhydrous ether to 0.021 g. of lithium in 5 ml. of ether) under an oxygen-free nitrogen atmosphere. The mixture was stirred for 2 hr. A solution of 0.25 g. of XVIII in 30 ml. of anhydrous ether was added to the mixture and stirring continued for an additional 4 hr. Ether was distilled as anhydrous tetrahydrofuran was added, until most of the ether had been displaced.[21] The reaction mixture was refluxed 6 hr., then allowed to stand at room temperature overnight. The mixture was diluted with 100 ml. of water and extracted with ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate; evaporation of the solvent yielded a gummy mass. Elution of this mixture through neutral alumina (30 g.) with 60 ml. of petroleum ether (b.p. 60–80°) followed by two recrystallizations from methanol yielded 0.220 g. (88.7%) of the olefin XXI, m.p. 57–58°. The analytical sample was obtained by recrystallization from the same solvent and had m.p. 60–61°, lit.[3] (for racemic compound) m.p. 54–55.5°; $\lambda_{\max}^{\text{KBr}}$ 3.73, 6.05, 11.3, and 11.45 μ; n.m.r. δ 0.80 (3), 0.83 (3), 0.93 (3), 4.44 (doublet J = 2 c.p.s., one proton), and 4.60 (broad, one proton).

Anal. Calcd. for $C_{20}H_{32}$: C, 88.16; H, 11.83. Found: C, 88.16; H, 11.73.

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