

Synthesis and Stereochemistry of Hydrophenanthrenes. V.

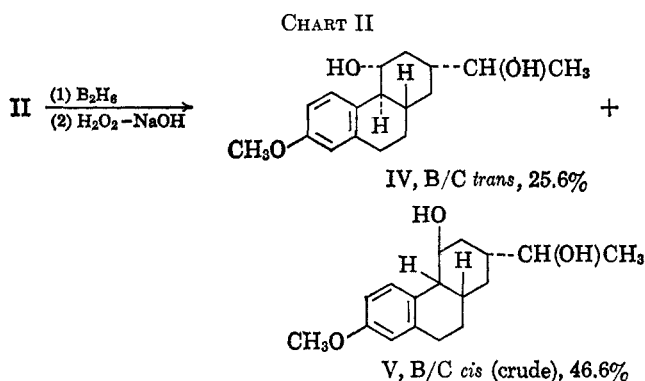
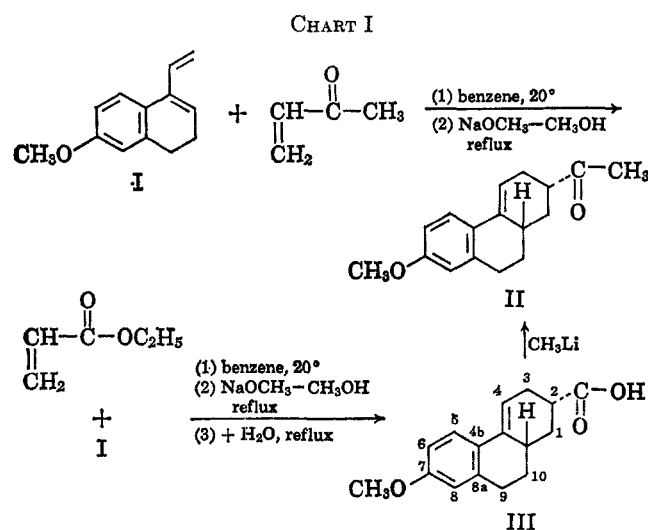
dl-2 α -Acetyl-1,2,3,4,4 α ,4 β ,5,6,7,9,10,10 β -Dodecahydro-4,7-dioxophenanthrene¹⁻³ZOLTAN G. HAJOS, CHRISTOPHER P. PARIOS, AND M. W. GOLDBERG⁴

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Received December 30, 1965

Hydroboration and oxidation of 2 α -acetyl-1,2,3,9,10,10 β -hexahydro-7-methoxyphenanthrene (II) gave the B/C *trans*-diol IV as the minor and the B/C *cis*-diol mixture V as the major reaction product. Lithium in liquid ammonia reduction of IV followed by hydrolysis and oxidation gave directly the *anti-trans* triketone XI. Upon identical treatment, the B/C *cis*-diol V gave the triketone mixture X. Inversion of the 4 α and 4 β centers was achieved by refluxing X with sulfuric acid in methanol to give the desired *anti-trans* triketone XI. The stereochemistry of the compound (XI) was confirmed by an independent synthesis starting with the already known *anti-trans* diketo acid XII.

In the course of the work aimed at the preparation of steroid-like compounds, the title compound (racemic *anti-trans* triketone XI) was synthesized. The starting material was 2 α -acetyl-1,2,3,9,10,10 β -hexahydro-7-methoxyphenanthrene (II), the *endo* addition product of the diene I with methyl vinyl ketone (Chart I). Its



relatively bulky diborane to the olefinic double bond by attack at the less hindered top side of the molecule (II). The stereochemical assignments are consistent with the well-established principles of hydroboration-oxidation,⁶ and also with the results obtained with the analogous acid III.⁵

Lithium in liquid ammonia reduction of the B/C *trans*-diol IV using a modified procedure,² gave the dihydro derivative VI in 86% yield. Hydrolysis of VI with refluxing hydrochloric acid in methanol gave a mixture of α,β - and β,γ -unsaturated keto diols VII (Chart III), which upon oxidation with chromium trioxide-sulfuric acid in acetone under nitrogen⁷ at -12° ,² gave the desired *anti-trans* triketone XI in 83.5% yield (Chart IV). The over-all yield of XI based on the B/C *trans*-diol IV was 71.5%.

The *anti-trans* configuration of the triketone XI is supported by the fact that it is recovered unchanged after equilibration with sodium methoxide in refluxing methanol. The assumed 4 β -configuration of the hydrogen is based on analogy with 19-norsteroids, where the β -configuration of the corresponding hydrogen was confirmed by optical rotatory dispersion studies.⁸ Furthermore, a 4 α -oriented hydrogen would force ring B into the energetically less favorable boat conformation.

Lithium in liquid ammonia reduction of the B/C *cis*-diol mixture V, using the modified procedure,² furnished the dihydro derivative VIII in 74% yield. Hydrolysis of VIII with refluxing hydrochloric acid in methanol gave a mixture of α,β - and β,γ -unsaturated diols IX, in 92% yield (Chart III). This mixture was oxidized with chromium trioxide-sulfuric acid in

preparation, stereochemistry, and stereochemical relationship to the unsaturated acid III have already been described.⁵ Hydroboration and oxidation⁶ of II gave a mixture of diols, which was separated by fractional crystallization into a less soluble fraction IV, mp 169–174° (25.6%), and a more soluble fraction V, mp 126–155° (46.6%) (Chart II). A new center of asymmetry was introduced in the 2 α -equatorial side chain during hydroboration. No attempt was made to establish the configuration of this center, the secondary alcohol in the side chain.

The minor hydroboration-oxidation product IV is obtained by *cis* addition of the diborane to the more hindered bottom side of the molecule (II). The major portion of the hydroboration-oxidation mixture, on the other hand, results from *cis* addition of the

(1) Presented at the First Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1966.

(2) Part IV: Z. G. Hajos, C. P. Parios, and M. W. Goldberg, *J. Org. Chem.*, **31**, 713 (1966).

(3) All compounds described are racemates. As a matter of convenience, only one enantiomeric series (10 $\alpha\beta$ -hydrogen) has been pictured.

(4) Deceased, Feb 17, 1964.

(5) Z. G. Hajos, D. R. Parrish, and M. W. Goldberg, *J. Org. Chem.*, **30**, 1213 (1965).

(6) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963).

(7) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(8) C. Djerassi, R. Riniker, and E. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

CHART III

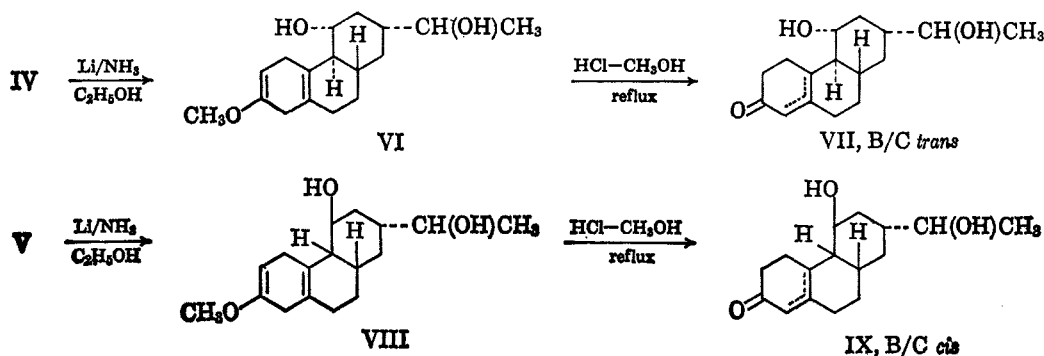


CHART IV

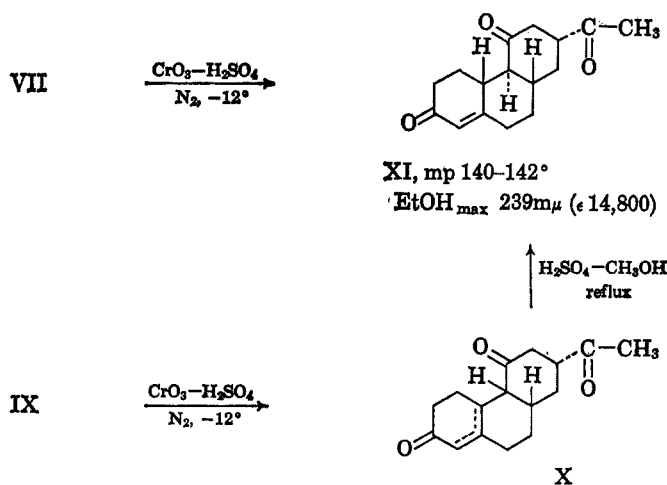
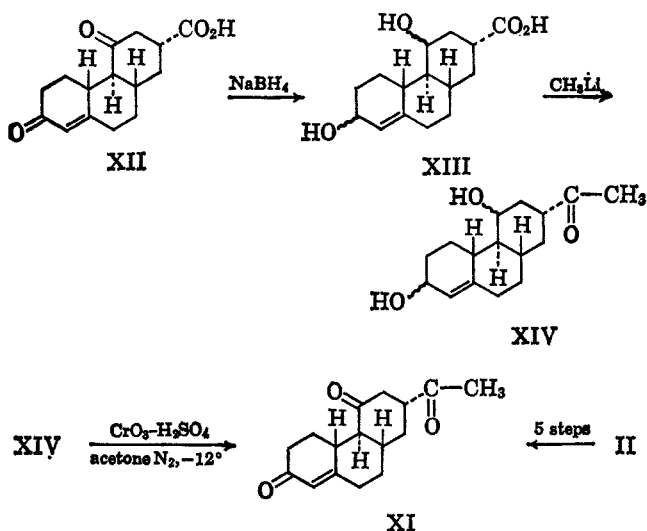


CHART V



acetone, under nitrogen⁷ at -12° to a mixture of α,β - and β,γ -unsaturated triketones X in 80% yield. Inversion of the 4a and 4b centers to give the *anti-trans* triketone XI in 44% yield was achieved by refluxing X with sulfuric acid in methanol (Chart IV). The compound was identical in every respect with the material obtained in the first synthesis. The over-all yield of XI, based on the B/C *cis*-diol V was 24%, after repeated equilibration of material from the mother liquors.

The stereochemistry of the *anti-trans* triketone XI was confirmed by an independent synthesis starting

with the previously described² *anti-trans* diketo acid XII. Sodium borohydride reduction gave the dihydroxy acid XIII. No attempt was made to establish the configuration of the hydroxyl groups. This compound, with methyllithium in tetrahydrofuran, gave the dihydroxy methyl ketone XIV. Oxidation at -12° under nitrogen² with chromium trioxide-sulfuric acid in acetone gave the *anti-trans*-triketone XI (Chart V). The compound XI was identical in every respect with the material obtained from the unsaturated methyl ketone II by the first synthesis.

Experimental Section⁹

Hydroboration and Oxidation of the Unsaturated Methyl Ketone (II).—The ketone II (51.2 g, 0.2 mole) was dissolved in 400 ml of anhydrous tetrahydrofuran (THF). The solution was stirred under nitrogen at 20° , and 420 ml of a THF solution containing 5.54 g of diborane⁶ was added over a period of 1 hr. This corresponds to 1 mole of diborane/mole of the unsaturated methyl ketone II. After standing at 20° under nitrogen for 16 hr, the solution was cooled in an ice bath, and ice was added carefully to destroy the excess diborane.

A sodium hydroxide solution (3.0 N, 143 ml) was added to the stirred ice-cold THF solution, and 70 ml of 30% hydrogen peroxide was then added over 15 min. The ice bath was removed, and the reaction was stirred at 20° for 1 hr. A freshly prepared solution of 78 g of sodium sulfite in 250 ml of water was added to destroy the excess peroxide. Most of the THF was removed *in vacuo*. The water solution was extracted with ethyl acetate and with ether, the extract was washed with brine, dried over

(9) All melting points were determined with a Thomas-Hoover melting point apparatus and are corrected. All ultraviolet spectra were taken in ethyl alcohol.

magnesium sulfate, filtered, and concentrated to about 400 ml. The crystalline precipitate was filtered, washed with ether, and dried *in vacuo* to give 14.14 g (25.6%) of diol fraction IV, mp 169–174°. Recrystallization from acetone gave the analytical sample: mp 172–174°; λ_{\max} 220 μ (ϵ 8800), 278 μ (ϵ 1820), 283 μ (ϵ 1620); ν_{\max}^{KBr} 3375, 3300, 1260–1350, and 1100 cm^{-1} (secondary alcohol bands).

Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{O}_3$: C, 73.88; H, 8.75. Found: C, 73.72; H, 8.44.

The filtrate from IV was concentrated *in vacuo* to about 200 ml and gave 25.72 g (46.6%) of a lower melting mixture V: mp 126–155°; λ_{\max} 220 μ (ϵ 8,600), 278 μ (ϵ 1950), 286 μ (ϵ 1600); ν_{\max}^{KBr} 3375, 3280, 1250–1375, 1130 cm^{-1} (secondary alcohol bands).

Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{O}_3$: C, 73.88; H, 8.75. Found: C, 74.04; H, 8.24.

Lithium in Liquid Ammonia Reduction and Hydrolysis of the Diols. A. From the Higher Melting Fraction IV.—The B/C *trans*-diol IV (16.0 g) was dissolved in 400 ml of absolute ethyl alcohol. The solution was cooled with a Dry Ice–acetone cooling mixture, and 800 ml of liquid ammonia was distilled into the system. Lithium wire (9.6 g), cut into *ca.* 160-mg pieces, was added through a special feeding device in 800-mg portions at -70° . No piece was added until after the blue from the preceding portion had disappeared. If the blue had not disappeared after 8–10 min, absolute ethyl alcohol was added dropwise to discharge the color. The total time for the addition of lithium was *ca.* 50 min. Absolute ethyl alcohol (50 ml) was added, and the Dry Ice–acetone bath was replaced with an acetone bath at room temperature. Ice–water (250 ml) was then added very slowly, while the ammonia was boiled off under nitrogen. The ethyl alcohol and the residual ammonia were then evaporated *in vacuo*, ice water (200 ml) was added, and the crystalline precipitate was filtered, and dried *in vacuo*. Recrystallization from acetone gave 13.85 g of the diol VI: mp 162.5–164.5°; λ_{\max} 278 μ (ϵ 76); ν_{\max}^{KBr} 3200–3500 cm^{-1} (hydroxyl groups), 1710, and 1685 cm^{-1} (dihydro anisole).

Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3$: C, 73.34; H, 9.41. Found: C, 73.52; H, 9.16.

The diol VI (12.5 g) was dissolved in 330 ml of methanol, 70 ml of 3 *N* hydrochloric acid was added, and the mixture was stirred and refluxed under nitrogen for 16 hr. The solution was then neutralized with 2 *N* sodium hydroxide, and concentrated *in vacuo* to about 50 ml. The residue was extracted thoroughly with ethyl acetate and then with ether. The combined extract was washed with brine, dried over magnesium sulfate, filtered, and evaporated *in vacuo* to give 11.72 g of VII, an amorphous glass, which was subjected to ultraviolet and infrared analyses only; λ_{\max} 240 μ (ϵ 12,000); ν_{\max}^{KBr} 3500 and 3350 (OH groups), 1680 cm^{-1} (α,β -unsaturated ketone).

B. From the Lower Melting Fraction V.—The B/C *cis*-diol mixture V (16.0 g) was reduced with lithium in liquid ammonia in the presence of ethyl alcohol, exactly as described under A, to give 12.21 g of diol VIII: mp 165–195°; no absorption in the ultraviolet; ν_{\max}^{KBr} 3200–3480 (OH band), 1710, and 1680 cm^{-1} (dihydro anisole).

Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3$: C, 73.34; H, 9.41. Found: C, 73.04; H, 9.26.

The diol VIII (11.7 g) was hydrolyzed with methanol and hydrochloric acid using the same conditions as described under A, for the isomeric diol VI to give 10.2 g of IX, an amorphous glass, which was subjected to ultraviolet and infrared analyses only: λ_{\max} 239 μ (ϵ 12,650); $\nu_{\max}^{\text{CHCl}_3}$ 3650 and 3600 (OH bands), 1650 cm^{-1} (α,β -unsaturated ketone).

dl-2 α -Acetyl-1,2,3,4,4 α ,4 β ,5,5,6,7,9,10,10 β -dodecahydro-4,7-dioxophenanthrene (XI). **A. From the B/C *trans*-Keto Diol VII.**—The keto diol VII (6.2 g) was dissolved in 275 ml of acetone. The solution was cooled to -12° and 11.3 ml of 8.0 *N* chromium trioxide–sulfuric acid solution was added dropwise to the stirred solution within 45 min. Ice–water (250 ml) was then added, and most of the acetone was removed *in vacuo*. The residue was extracted with ethyl acetate and then with ether. The combined extract was washed with brine, dried over magnesium sulfate, filtered, and evaporated *in vacuo* to give 5.18 g (83.7%) of the crude trione XI, mp 138–140°. Recrystallization from acetone–hexane gave the analytical sample: mp 140.5–142.5°; λ_{\max} 239 μ (ϵ 14,350); ν_{\max}^{KBr} 1715 (saturated ketones), 1680 (α,β -unsaturated ketone), 1618 cm^{-1} (C=C double bond).

Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$: C, 73.82; H, 7.74. Found: C, 73.54; H, 7.94.

B. From the B/C *cis*-Keto Diol Mixture IX.—Compound IX (10 g) dissolved in 425 ml of acetone was oxidized at -12° with 19.3 ml of 8.0 *N* chromium trioxide–sulfuric acid solution as described for VII under A, to give 8.63 g (86.5%) of the trione mixture X: mp 112–135°; λ_{\max} 239 μ (ϵ 14,250); ν_{\max}^{KBr} 1710 (saturated ketone), 1670 (α,β -unsaturated ketone), 1610 cm^{-1} (C=C double bond).

Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$: C, 73.82; H, 7.74. Found: C, 73.62; H, 7.80.

The trione mixture X (8.63 g) was refluxed with 200 ml of 2.0 *N* sulfuric acid in methanol for 1 hr. The solution was cooled with an ice bath and neutralized with 2.0 *N* sodium hydroxide. Most of the methanol was then evaporated *in vacuo* and the remaining solution was extracted with ethyl acetate and then with ether. The extract was washed with brine, dried over magnesium sulfate, filtered, and evaporated *in vacuo*. The residue was treated with ether, and the ether insoluble crystalline material was recrystallized from acetone to give 1.5 g of the pure *anti-trans* trione XI, which was identical in every respect with the preparation described under A.

The rest of the material (the acetone- and ether-soluble fractions) was re-treated with refluxing 2.0 *N* sulfuric acid in methanol, as already described. An additional 2.3 g of the pure *anti-trans* trione XI was thus obtained, mp 140.5–142.5°. The total yield of XI based on X was 44%.

C. From the *anti-trans* Diketo Acid XII.—The acid XII (512 mg) was dissolved in 20 ml of 0.1 *N* sodium hydroxide. The solution was cooled to 0° and 67 mg of sodium borohydride was added to the stirred solution. It was then allowed to come up to 20° . It was stirred at this temperature for 16 hr. It was then acidified with 0.5 *N* hydrochloric acid to pH 3.0. The resulting crystalline precipitate was filtered off, and dried *in vacuo* at 65° for 16 hr to give 404 mg of the dihydroxy acid XIII: mp 186° dec; the compound showed no ultraviolet absorption; infrared absorption, $\nu_{\max}^{\text{CHCl}_3}$ 3200–3400 (hydroxyl bands), 2500–2700 (associated hydroxyl of acid), and 1700 cm^{-1} (acidic carbonyl).

The dihydroxy acid XIII (403 mg) was dissolved in 40 ml of anhydrous tetrahydrofuran. The solution was stirred under nitrogen and 11.4 ml of a 1.6 *N* methylolithium solution in ether was added within 2 hr at 20° . Stirring was continued for 16 hr at 20° , then it was refluxed for 5 hr. The solution was then added slowly to ice–water, and most of the solvent was evaporated *in vacuo*. The aqueous residue was extracted with ethyl acetate. The extract was washed with a dilute sodium bicarbonate solution and then with water, dried with magnesium sulfate, and evaporated *in vacuo* to give 314 mg of an amorphous solid dihydroxy methyl ketone XIV: $\nu_{\max}^{\text{CHCl}_3}$ 3200–3400 (hydroxyl bands), and 1710 cm^{-1} (ketone carbonyl).

The dihydroxy ketone XIV (304 mg) was dissolved in 20 ml of acetone. The solution was cooled to -12° , and 0.58 ml of an 8.0 *N* chromium trioxide–sulfuric acid solution was added within 6 sec, under a strong stream of nitrogen and with vigorous stirring. After stirring for 12 min at -12° , an ice-cold solution of sodium chloride in water was added, and most of the acetone was removed *in vacuo*. The residue was extracted with ethyl acetate. The extract was washed with brine, then with ice–water, dried over magnesium sulfate, and evaporated *in vacuo* to give 209.4 mg of crude XI: λ_{\max} 239 μ (ϵ 9700). The ether-insoluble crystalline material was recrystallized from acetone to give the pure *anti-trans* triketone XI, which was identical in every respect with the preparation described under A.

Equilibration of the *anti-trans* Triketone XI with Sodium Methoxide in Methanol.—The triketone XI (360 mg) was refluxed in 15 ml of 2.3 *N* sodium methoxide in methanol under nitrogen for 22 hr. The solution was cooled to 20° and neutralized with 2.0 *N* hydrochloric acid. Water (20 ml) was added, and most of the methanol was evaporated *in vacuo*. The aqueous residue was extracted with ethyl acetate and then with ether. The extract was washed with brine, dried with magnesium sulfate, filtered, and evaporated *in vacuo*. The residue was treated with ether, and the ether-insoluble crystalline material was filtered to give 330 mg of the *anti-trans* triketone XI, which was identical in every respect with the starting material.

Acknowledgment.—The authors wish to express their thanks to Dr. V. Toome for the ultraviolet and to Mr. S. Traiman for the infrared spectroscopic data, and to Dr. A. Steyermark for the microanalyses.