Cassaine Analogs. III. Synthesis of *dl*-15,16,17,20-Tetranorcassaine

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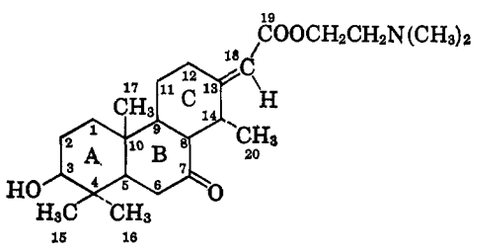
Cunninghamella bainieri has been used to hydroxylate decahydrophenanthrone **2**. Two products, **12** and **13**, were isolated. Treatment of β-hydroxy ketone **12** with acid afforded diketone **14**, which was used to prepare the title compound (**24**) as well as its geometric isomer (**25**). The basis for assignment of configuration to these geometric isomers is presented.

Cassaine (**1**), an alkaloid found in the bark of the African tree *Erythrophleum guineense* (G. Don), exerts an action on the heart similar to that produced by digitalis.[1] We found it of interest to determine the effect of various changes in the configuration and functional groups of cassaine on its biological activity. In paper I[2] of this series the synthesis of various tricyclic ketone precursors including perhydrophenanthrones



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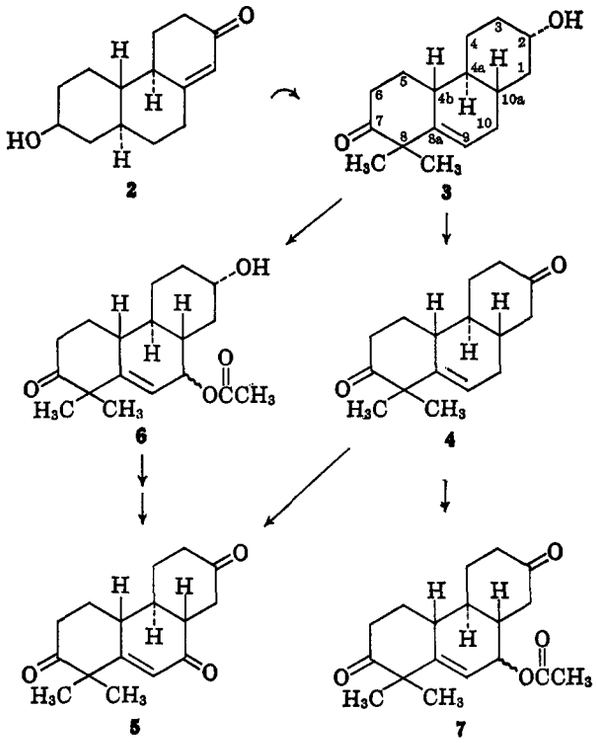
having *cis-anti-trans*, *trans-anti-cis*, and *trans,anti,trans* configurations was described. In paper II[3] the conversion of these ketones to basic ester analogs of cassaine was described. Since none of these synthetic analogs incorporated the C-7 oxygen function found in cassaine, it was desirable to prepare such compounds for evaluation. The present paper describes a chemical and then a microbiological approach to the introduction of the ring B oxygen.

Dimethylation of *dl*-4,4aα,4bβ,5,6,7,8,8aα,9,10-decahydro-7β-hydroxy-2(3H)-phenanthrone (**2**)[2] afforded dimethyl ketone **3**. Chromium trioxide–pyridine oxidation of **3** gave diketone **4**. (See Scheme I.) The allylic position at C-10 (phenanthrene numbering) was then oxidized with *t*-butyl chromate to give triketone **5**, but the yield was poor.

Not satisfied with this yield, we used *t*-butyl peracetate in the presence of copper(I) ion[4] to effect the desired allylic oxidation. When carried out on hydroxy ketone **3** and diketone **4**, this reaction furnished **6** and **7**, each as an epimeric mixture at C-10. However, the yields were again low. Oxidation could have occurred at the other allylic position (4b) in both methods of oxidation, perhaps the cause of the low yields. No other pure product was isolated.

Without separation of the C-10 epimers, the acetate mixture **6** was saponified and oxidized to afford triketone **5**. The over-all yield to this point was low.

SCHEME I



Hydrogenation of the 8a,9 double bond was expected to give a mixture of A/B-*cis* and A/B-*trans* isomers,[5] a factor which would further limit available material. It was decided at this juncture to leave the double bond in the molecule for the remainder of the synthesis in the hope that it would not materially affect biological activity.

Treatment of triketone **5** with the phosphonium ylid obtained from the reaction of trimethyl phosphonoacetate and sodium methoxide gave a mixture of isomeric α,β-unsaturated methyl esters **8** and **9** in good yield. (See Scheme II.) The conditions used precluded the possibility of the reagent's having attacked the hindered C-7 ketone or the conjugated C-10 ketone.[3,6]

Preparative thin layer chromatography (tlc) on silica gel permitted the separation of this mixture of double bond isomers. The *trans* structure, shown by formula **8**, is defined as that in which the carboxyl group is *trans* to the "bulge of ring B." Thus, **9** is the *cis* form. The basis for assignment of structure to the two isomers isolated will be discussed later. It is interesting to note that *cis–trans* mixtures in the cassaic acid series,[6] which have an oxygen in ring B, can also be

(1) See F. Erjavec and Š. Adamič, *Arch. Intern. Pharmacodyn.*, **155**, 251 (1965); E. L. McCawley in "The Alkaloids," Vol. V, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1955, pp 101–107, and references therein.

(2) S. J. Daum, P. E. Shaw, and R. L. Clarke, *J. Org. Chem.*, **32**, 1427 (1967).

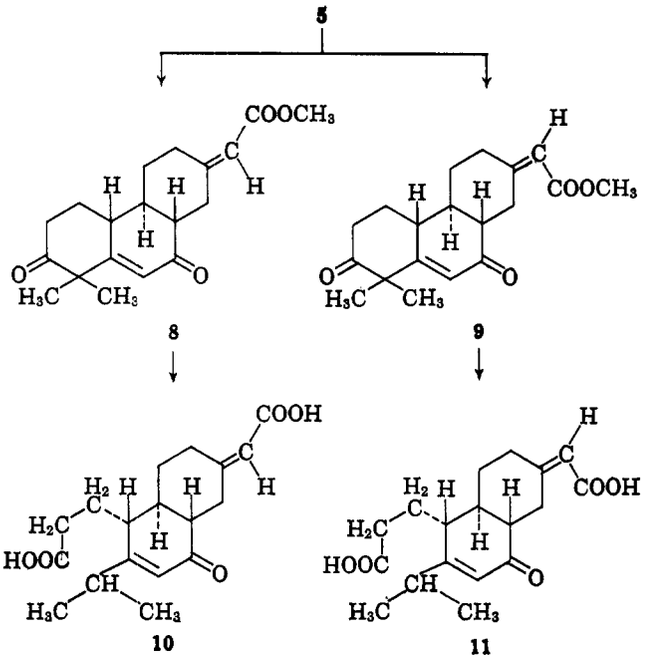
(3) R. L. Clarke, S. J. Daum, P. E. Shaw, T. G. Brown, Jr., G. E. Groblewski, and W. V. O'Conner, *J. Med. Chem.*, in press.

(4) G. Sosnovsky and S. O. Lawesson, *Angew. Chem. Intern. Ed. Engl.*, **3**, 269 (1964).

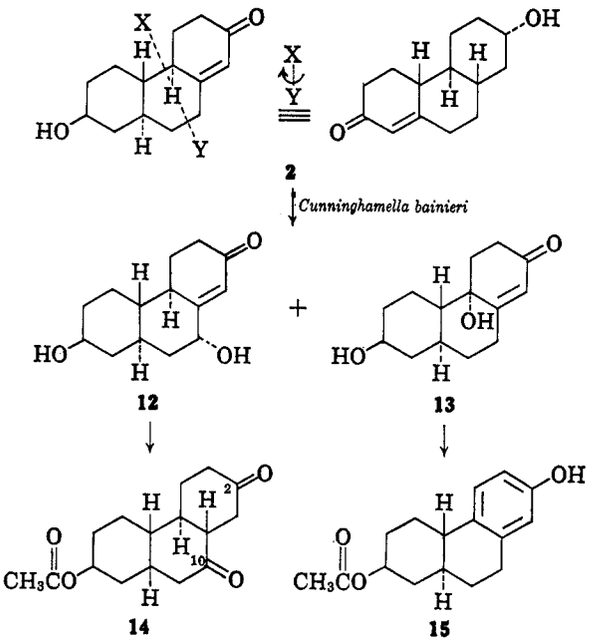
(5) J. M. Midgley, W. B. Whalley, G. F. Katekar, and B. A. Lodge, *Chem. Commun.*, 169 (1965).

(6) R. L. Clarke, S. J. Daum, P. E. Shaw, and R. K. Kullnig, *J. Am. Chem. Soc.*, **88**, 5865 (1966).

SCHEME II



SCHEME III



separated by tlc on silica gel but that ring-B deoxy analogs[3,7] show no separation at all.

When esters **8** and **9** were treated with refluxing aqueous sodium hydroxide, not only was the ester group saponified but the anticipated retroaldol condensation of the vinylogous β-diketone occurred to give dibasic acids **10** and **11**, respectively.

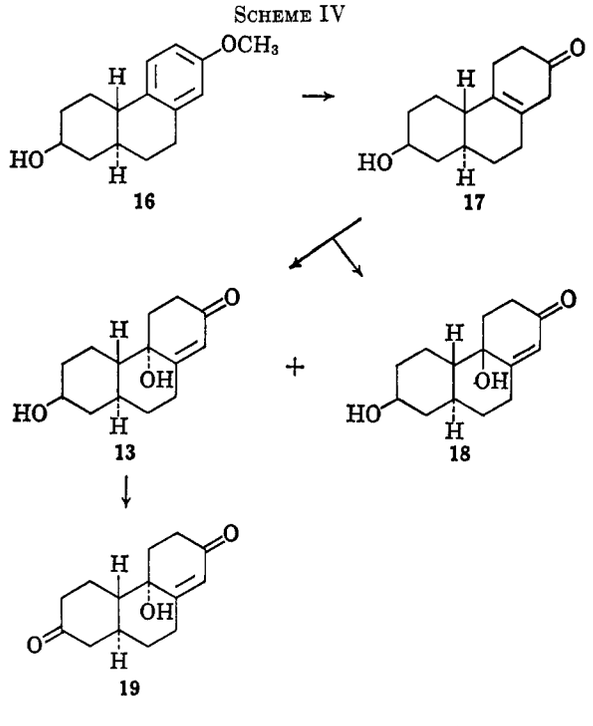
Since it was found at this point that ring-B hydroxylation could be achieved with microbes, we set aside the above approach and continued with this much simpler course.

Structure **2** is quite similar to a Δ^4-3-keto steroid, a system which lends itself readily to 6β hydroxylation by a host of organisms.[8] Incubation of **2** with the organism *Cunninghamella bainieri* afforded two major products, **12** and **13**. (See Scheme III.)

The structure of **12**, the desired product, was supported by its ultraviolet[9] absorption characteristics and confirmed by its acid-catalyzed conversion to diketone **14**. The second compound was assigned structure **13** when it was found to be identical with the major product obtained in a reaction described immediately below. As expected, it produced phenol **15** in the presence of acid.

Phenanthrol **16**[2] was reduced with lithium in ammonia and the resulting enol ether was hydrolyzed with oxalic acid to afford the β,γ-unsaturated ketone **17**. The reaction of this unsaturated ketone with *m*-chloroperbenzoic acid followed by silica gel chromatography of the crude mixture of epoxides afforded dihydroxy compounds **13** and **18**, the silica gel's having opened the epoxide rings. (See Scheme IV.) The assignment of configuration to the angular hydroxyl groups is based on steroid precedent.[10]

SCHEME IV

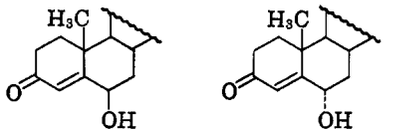


The positions hydroxylated in **2** by *C. bainieri* are sterically similar to the positions of hydroxylation reported recently by Smith, Greenspan, Reese, and Foell[11] from the action of *Aspergillus ochraceus* on *dl*-testos-

(7) R. L. Clarke, S. J. Daum, P. E. Shaw, T. G. Brown, Jr., G. E. Groblewski, and W. V. O'Conner, *J. Med. Chem.*, in press.

(8) R. I. Dorfman and F. Unger, "Metabolism of Steroid Hormones," Academic Press Inc., New York, N. Y., 1965, p 230, and references therein.

(9) A 6β-hydroxyl group (axial) causes a hypsochromic shift in the absorption wavelength of Δ^4-3-keto steroids as well as a lowering of the extinction coefficient. The 6α epimer produces no such shift (i *vs.* ii); see L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 203, and references cited.



λ 237 mμ (ε 14,500) i

λ 240 mμ (ε 17,000) ii

(10) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956); J. P. Ruelas, J. Iriarte, F. Kincl, and C. Djerassi, *J. Org. Chem.*, **23**, 1744 (1958); F. B. Colton, U. S. Patent 2,729,654 (1956).

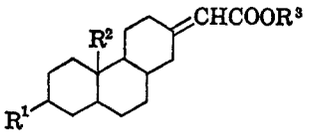
(11) L. L. Smith, G. Greenspan, R. Reese, and T. Foell, *J. Am. Chem. Soc.*, **88**, 3120 (1966).

TABLE I

COMPARISON OF PHYSICAL PROPERTIES OF *cis* AND *trans* ISOMERS

Compd		Extinction coefficient		Tlc R_f value		Glpc retention time	
cis	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
Cassaic acid series[a]		16,300[b]	17,200[b]	Lower	Greater	Less	Greater
From present paper							
9	**8**	20,900	21,600	Lower	Greater	Greater	Less
11	**10**	18,200	20,600	Lower	Greater	Not volatile	
21	**20**	16,900	18,400	Lower	Greater	Greater	Less
23	**22**	15,000	16,200	Lower	Greater	Not volatile	
25	**24**	16,200	18,300	Lower	Greater	...	...
10-Desoxy series[c]							
A[d]	B[d]	15,400	16,200	No difference		Not volatile	
C[d]	D[d]	16,100	16,200	No difference		Not volatile	
E[d]	F[d]	15,300	16,100	No difference		Not volatile	
G[e]	H[e]	17,400	18,300	No difference		Less	Greater
I[e]	J[e]	17,700	18,600	No difference		Less	Greater

[a] Reference 6. [b] Average values. [c] Phenanthrene numbering, ref 3. See footnote formula below for structures. [d] Reported in Table II of ref 3. [e] Reported in Table III of ref 3.

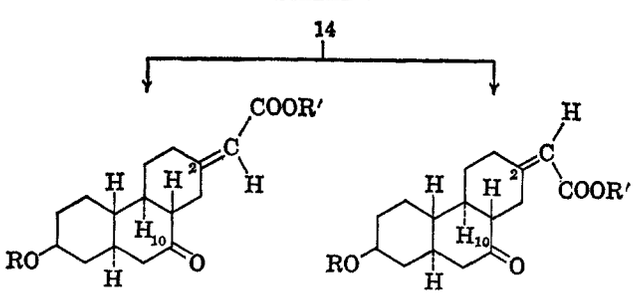


A and B, R^1 = O; R^2 = H; R^3 = H
C and D, R^1 = O; R^2 = CH_3; R^3 = H
E and F, R^1 = β-OH; R^2 = CH_3; R^3 = H
G and H, R^1 = O; R^2 = H; R^3 = $CH_2CH_2N(CH_3)_2$
I and J, R^1 = β-OH; R^2 = CH_3; R^3 = $CH_2CH_2N(CH_3)_2$

terone. Compound **13** was oxidized to hydroxy diketone **19** which was used as a precursor to one of the basic esters described in paper II.[3]

Treatment of diketone **14** with the phosphonium ylid obtained from the reaction of trimethyl phosphonoacetate with sodium methoxide afforded a mixture of α,β-unsaturated methyl esters **20** and **21** in good yield. (See Scheme V.) That the reaction occurred at position 2 and not at position 10 was well established for a similar diketone.[6] Again we could separate the *cis* (**21**) and *trans* (**22**) double-bond isomers using preparative thin layer chromatography.

SCHEME V



20, R = Ac; R′ = CH_3
22, R = R′ = H
24, R = H; R′ = $CH_2CH_2N(CH_3)_2$

21, R = Ac; R′ = CH_3
23, R = R′ = H
25, R = H; R′ = $CH_2CH_2N(CH_3)_2$

Saponification of esters **20** and **21** afforded the corresponding acids **22** and **23**. Acid **22** was converted to *dl*-15,16,17,20-tetranorcassaine (**24**) by treatment of its sodium salt with oxalyl chloride followed by dimethylaminoethanol. This base was characterized as its hydrochloride salt. Acid **23** was converted in a similar fashion to the hydrochloride salt of basic ester **25**.

Basic esters **24** and **25** have considerably less cardiotonic activity than cassaine.[12]

The question of assignment of configuration to the *cis vs. trans* isomers about the exocyclic double bond in the presently reported series and in paper II[3] cannot be answered unequivocally with available data. The configurations of several pairs of such isomers were established firmly in the process of proving the structure of cassaic acid.[6] There it was shown that the *trans* isomer had the higher ultraviolet extinction coefficient, the larger tlc R_f value, and the longer retention time in gas–liquid partition chromatography (glpc).

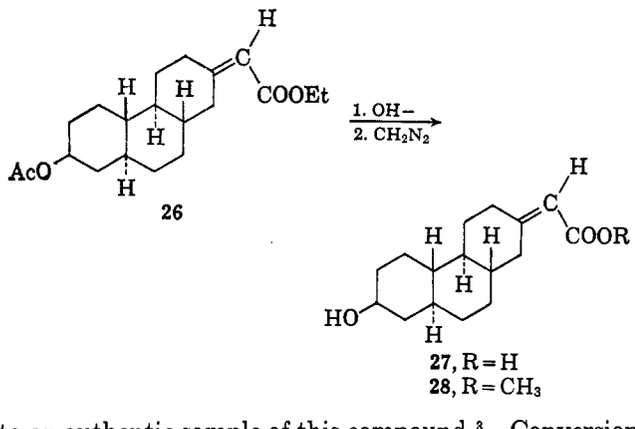
In the present work, five pairs of isomers have been isolated. Table I summarizes the ultraviolet absorption data, the relative polarities by tlc, and the relative retention times by glpc of these compounds. Of the three properties being considered, the ultraviolet absorption coefficient is probably the most reliable indicator of the structural environment of the chromophore. If by analogy with the cassaic acid derivatives,[6] we assign the *trans* configuration to that isomer of each pair with the higher ε value, we see that the relative R_f values by tlc follow the same pattern as in the cassaic acid series. There is, however, a reversal in the glpc retention times. Such reversals are not unexpected but this circumstance in the present instance does produce a degree of uncertainty about the chosen assignment.

Turning to the *cis* and *trans* pairs of isomers described in paper II,[3] there was no observed difference in R_f value between the two isomers (see Table I). Although the steric environment of the chromophore is nearly symmetrical in this series which has no oxygen in ring B, it was observed that four of the five pairs of isomers studied showed significant differences in ultraviolet absorption intensity (Table I). In both cases

(12) The pharmacological studies are reported in ref 3 and 7.

where the compounds were volatile (G and H and I and J), the isomers with the higher extinction coefficient (H and J) had the greater glpc retention time. The acids derivable from H and J also showed higher ϵ values than their isomers did. We conclude that the ultraviolet absorption properties and glpc retention order in this ring-B deoxy series probably parallel the findings in the cassaic acid series.

It appeared useful, then, to try to relate the series presently reported with the ring-B deoxy series by finding out if an assigned *cis* isomer in one series gave the assigned *cis* product in the other series. To this end, the ethyl ester (R = OAc, R′ = C_2H_5) of *cis* acid **23** (containing perhaps 10–15% *trans* isomer) was converted into its ethylenedimercapto derivative which was desulfurized with deactivated Raney nickel. Unfortunately, hydrogenation occurred along with desulfurization and only a very small quantity of deoxyunsaturated ester **26** was obtained. It was hydrolyzed to give an oily acid (**27**) which corresponded in R_f value



26

27, R = H
28, R = CH_3

to an authentic sample of this compound.[3] Conversion of **27** to ester **28** by means of diazomethane produced an oily ester which corresponded in R_f value to an authentic sample of **28**. Glpc analysis showed that the crude ester, purified only by tlc, contained approximately 42% of material with a retention time matching that of authentic *cis* ester **28**, 48% of an unknown substance, and 10% of material with a retention time equal to that of the *trans* isomer corresponding to **28**. The information from this conversion is certainly limited and no more material was available for study. However, it does give indication that the configurational assignments based on extinction coefficients do correspond in the two series under discussion.

On the basis of the information presented, we have provisionally assigned the *trans* configuration to that isomer in each pair which has the higher ultraviolet extinction coefficient. In the large series of unseparated isomer mixtures reported in paper II,[3] we have assigned the *trans* configuration to that isomer with the greater retention time. This is in accord with glpc characteristics of the compounds of this same series which were given assignment on the basis of ϵ value. In the case of compounds C and D of Table I which have essentially the same ϵ values, the assignment was based on the glpc retention times of the nearly pure ethyl ester precursors.[3]

Experimental Section[13]

***dl*-1,2,3,4,4aα,4bβ,5,6,7,8,10,10aβ-Dodecahydro-8,8-dimethyl-7-oxo-2α-phenanthrol (3).**—A solution of 27.4 g (0.125 mole) of *dl*-4,4aα,4bβ,5,6,7,8,8aα,9,10-decahydro-7β-hydroxy-2(3H)-phenanthrone (**2**)[2] in 600 ml of *t*-butyl alcohol was treated with 35.0 g (0.310 mole) of potassium *t*-butoxide. The reaction mixture was flushed with nitrogen and methyl iodide (70 g, 0.50 mole) was added over a period of 30 min. The solution, which now contained a precipitate, was stirred at room temperature for 1 hr, then heated under reflux for 10 min. The reaction mixture was cooled, dilute hydrochloric acid and ether were added, and the layers were separated. The ether layer was washed with dilute sodium hydroxide solution and then with saturated sodium chloride solution. It was dried (Na_2SO_4) and evaporated to afford an oily residue which crystallized from ether containing hexane. Two recrystallizations from the same solvent gave 11.0 g of **3**, mp 116–118°. Upon concentration of the mother liquor, another crop of 3.2 g, mp 114–116°, was obtained. The mother liquor residue was chromatographed on 500 g of silica gel. Elution with methylene dichloride–ether–pentane (2:5:3) afforded another 5.5 g of **3**, mp 116–117° (64%). The nmr spectrum ($CDCl_3$) had peaks at δ = 1.23 (singlet 6 H, CH_3) and 5.5–5.8 ppm (multiplet, 1 H, vinyl). The analytical sample from ether containing hexane melted at 121–122°.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.39; H, 9.74. Found: C, 77.8; H, 9.7.

***dl*-3,4,4aα,4bβ,5,6,7,8,10,10aβ-Decahydro-8,8-dimethyl-7-oxo-2(1H)-phenanthrone (4).**—A solution of 16.6 g (0.067 mole) of hydroxy ketone **3** in 210 ml of pyridine was added to 210 ml of pyridine containing 16.6 g (0.166 mole) of chromium trioxide. The mixture was stirred overnight and was then added to about 700 ml of ethyl acetate. The mixture was filtered through Supercel and the solvent was removed by warming *in vacuo*. Ether was added to the residue and more inorganic solids were filtered away. The ether was concentrated to afford 11.9 g of **4**, mp 130–133°, and a second crop of 1.21 g, mp 128–130°. The mother liquor residue was chromatographed on 150 g of silica gel. Elution with methylene dichloride–ether–pentane (2:3:5) afforded another 0.7 g, mp 131–133° (83%). The analytical sample (from ether) melted at 133–134°.

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.02; H, 9.00. Found: C, 78.2; H, 9.1.

Mixture of *dl*-10α- and -10β-Acetoxy-3,4,4aα,4bβ,5,6,7,8,10,10aβ-decahydro-8,8-dimethyl-7-oxo-2(1H)-phenathrones (7).—A solution of 250 mg (1.0 mmole) of diketone **4** in 5 ml of benzene and 1 ml of glacial acetic acid was treated with 0.17 ml (1.0 mmole) of *t*-butyl peracetate (75% in benzene). Cuprous chloride (1 mg) was added and oxygen was removed from the reaction mixture by flushing it with nitrogen. The solution was heated under reflux in an atmosphere of nitrogen for 22 hr. At this time thin layer chromatography (tlc) of an aliquot indicated that the reaction was about 60% complete. Another 0.17 ml (1.0 mmole) of *t*-butyl peracetate and a trace of cuprous chloride were added. After the reaction mixture was heated under reflux for another 7 hr, the above addition procedure was repeated. The reaction mixture was then heated under reflux for 24 hr. Tlc indicated that the reaction was incomplete. The reaction mixture was added to ice–water. Ether was added and the layers were separated. The ether was washed with saturated sodium bicarbonate and saturated sodium chloride solutions and then dried (Na_2SO_4). Evaporation of the solvent afforded an oily residue that was redissolved in ether and the solution was filtered. Evaporation of the solvent by warming *in vacuo* gave 190 mg of an oily residue. The residue was chromatographed on 19 g of silica gel. Elution with 400 ml of methylene dichloride–ether–pentane (2:3:5) gave 50 mg (20%) of starting diketone **4** which was identified by melting point and tlc. Continued elution with another 60 ml of the same solvent mixture afforded 60 mg (20%) of the mixture of acetates **7**; nmr peaks at δ = 5.05 and 5.94 ppm (=CH, doublets, not sharp, intensity ratio about 6:4). The signals for the C-10 hydrogen were registered on the integrator curve in this same region but could not be clearly identified. The signal at δ = 2.05 ppm (CH_3COO) has two peaks (separated by 2 Hz) which reflect the same intensity ratio (6:4).

(13) All melting points are corrected. The infrared spectra were recorded on a Perkin-Elmer infrared spectrophotometer, Model 21, unless otherwise noted. The ultraviolet spectra were recorded on a Cary spectrophotometer, Model 15. The nmr spectra were recorded on a Varian A-60 nmr spectrometer. Solutions (10–20%) were used with TMS as an internal standard (TMS = 0 ppm). Silica gel G, purchased from Brinckmann Instruments Inc., was used for thin layer chromatography. Silica gel PF 254, from the same supplier, was used for preparative thin layer chromatography.

Tlc (methyl alcohol–ether, 1:49) did not separate the components of this mixture.

Mixture of *dl*-10α- and -10β-Acetoxy-1,2,3,4,4aα,4bβ,5,6,7,8,-10,10aβ-dodecahydro-8,8-dimethyl-7-oxo-2α-phenanthrol (6).—A solution of 2.3 g (9.3 mmoles) of hydroxy ketone **3** in 50 ml of benzene and 5 ml of acetic acid was treated with 1.7 ml (10.0 mmoles) of *t*-butyl acetate (75% in benzene). Cuprous chloride (10 mg) was added and the reaction flask, after being flushed with nitrogen, was boiled under reflux in a nitrogen atmosphere for 24 hr. Tlc indicated that the reaction was incomplete. Another 2 ml of *t*-butyl peracetate was added and the reaction mixture was boiled under reflux for another 24 hr. The reaction mixture was worked up as described above. The oily residue (2.65 g) was chromatographed on 200 g of silica gel. Elution with methylene dichloride–ether–pentane (2:3:5) afforded 540 mg (23%) of starting material **3**. Continued elution with methylene dichloride–ether (1:4) then gave 690 mg (19%) of the desired mixture of acetates (**6**) which was used without characterization.

***dl*-3,4,4aα,4bβ,5,6,7,8,10,10aβ-Decahydro-8,8-dimethyl-7,10-dioxo-2(1H)-phenanthrone (5). Procedure A.**—Acetates **6** (690 mg, 2.25 mmoles) and acetates **7** (20 mg, 0.06 mmole) were combined and dissolved in 30 ml of 5% methanolic potassium hydroxide containing 5% water. The solution was boiled under reflux in a nitrogen atmosphere for 0.75 hr, cooled, and added to ice and water. Sodium chloride was added followed by ether. The layers were separated and the ether layer was washed twice with saturated sodium chloride solution. The aqueous layers were washed with a fresh portion of ether and the combined ether layers were then dried (Na_2SO_4) and concentrated by warming *in vacuo* to afford 390 mg of an oily residue.

The residue was dissolved in 20 ml of pyridine and this solution was added all at once to 20 ml of pyridine containing 600 mg of chromium trioxide. After sitting at room temperature for 40 hr, the reaction mixture was added to about 100 ml of ethyl acetate and the resulting mixture was filtered through Supercel. The filtrate was warmed *in vacuo* to remove the solvent. Ether was added and more inorganic solids were filtered away. The ether was evaporated and the residue was crystallized from ether to give 140 mg (23%) of **5**, mp 147–150°. Recrystallization from ether afforded 110 mg: mp 152–153°, λ_{max}^{EtOH} 242 mμ (ε 11,500).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.83; H, 7.76. Found: C, 74.1; H, 7.9.

Procedure B.—A solution of 19 ml of *t*-butyl chromate in carbon tetrachloride,[14] 20 ml of carbon tetrachloride, 6 ml of acetic acid, and 2.5 ml of acetic anhydride was heated at 50° in a water bath. A slow stream of air was blown through the stirred solution. A solution of 1 g (4.1 mmoles) of diketone **4** in 18 ml of carbon tetrachloride was added during a 0.5-hr period. The temperature was maintained at 50–70° for a 2-hr period. This solution was stirred at room temperature with a slow stream of air passing through for another 16 hr. Carbon tetrachloride (50 ml) was added to the reaction mixture (to maintain volume). Oxalic acid (7.5 g, 83 mmoles) in 75 ml of water was added during a 0.5-hr period, while the solution was being stirred in an ice bath. Oxalic acid (5.25 g) was added and the reaction mixture was stirred for another 2 hr. More carbon tetrachloride and water were added and the layers were separated. The aqueous layer was washed with a fresh portion of carbon tetrachloride. The carbon tetrachloride solutions were combined and washed twice with saturated sodium bicarbonate and once with saturated sodium chloride solution. The organic solution was dried (Na_2SO_4) and the solvent was removed by warming *in vacuo* to afford 320 mg of a residue. The aqueous layers were extracted with ethyl acetate and gave another 570 mg of oily residue upon evaporation. Crystallization from ether afforded 225 mg (21%) of **5**: mp 148–151°, λ_{max}^{EtOH} 243 mμ (ε 11,100).

Preparation of *cis*- and *trans*-Unsaturated Esters 9 and 8.—A solution of 46 mg (0.85 mmole) of sodium methoxide in 5 ml of dimethylformamide (DMF) was treated with 155 mg (0.85 mmole) of trimethylphosphonoacetate in 5 ml of DMF. The reaction mixture was stirred in an ice bath for 5 min and 110 mg (0.43 mmole) of triketone **5** in 10 ml of DMF was added all at once. The solution was stirred at room temperature for 15 min and was then added to ice and water. This mixture was made acidic with dilute hydrochloric acid, chilled, and extracted with ether. The ether was washed with saturated sodium chloride solution. The aqueous layers were extracted with a fresh portion of ether. The combined ether layers were dried (Na_2SO_4) and concentrated to a residue that was chromatographed on a silica gel coated plate (40 × 20 cm) having a 1-mm coating. Eight passes with an ether–pentane (1:1) solvent mixture were needed for proper development. The more polar band from the plate (eluted with acetone) afforded 50 mg (40%) of **methyl *dl*-*cis*-3,4,4aα,4bβ,5,6,7,8,10,-10aβ-decahydro-8,8-dimethyl-7,10-dioxo-Δ$^{2(1H),\alpha}$-phenanthreneacetate (9)**. The analytical sample, obtained from ether, melted at 142–143°; λ_{max}^{EtOH} 223 mμ (ε 20,900).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.3; H, 7.7.

The less polar band from the plate (eluted with acetone) afforded 50 mg (40%) of **methyl *dl*-*trans*-3,4,4aα,4bβ,5,6,7,8,10,-10aβ-decahydro-8,8-dimethyl-7,10-dioxo-Δ$^{2(1H),\alpha}$-phenanthreneacetate (8)**. The analytical sample, obtained from ether, melted at 123–124°; λ_{max}^{EtOH} 223 mμ (ε 21,600).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.3; H, 7.7.

***dl*-5α-(2-Carboxyethyl)-3,4,4aα,5,8,8aβ-hexahydro-6-isopropyl-8-oxo-Δ$^{2(1H),\alpha}$-naphthaleneacetic Acid (Isomer A, 10).**—Unsaturated ester **8** (810 mg, 2.5 mmoles) in 20 ml of ethanol and 8 ml of 2 *N* sodium hydroxide was boiled under reflux in a nitrogen atmosphere for 1 hr. The reaction mixture was added to ice–water and the solution was made acidic with dilute hydrochloric acid. Sodium chloride was added to the reaction mixture which was then extracted with ether. The extract was dried (Na_2SO_4) and concentrated to afford 810 mg of residue. The residue was chromatographed on 100 g of silica gel. Elution with acetic acid–ether–pentane (3:50:47) afforded 230 mg of **10**, mp 186–190°. Recrystallization from ether gave crystals that melted at 194–195°; λ_{max}^{EtOH} 229 mμ (ε 20,600); nmr (DMSO-d_6), peaks at δ = 0.83–1.2 (6 H, two doublets, methyls), 5.6 and 5.7 ppm (2 H, two singlets, vinyl hydrogens). Recovery of the nmr sample and recrystallization from ether afforded the analytical sample that melted at 186–188°.

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.47; H, 7.58; neut equiv, 160.7. Found: C, 67.5; H, 7.8; neut equiv, 162.

***dl*-5α-(2-Carboxyethyl)-3,4,4aα,5,8,8aβ-hexahydro-6-isopropyl-8-oxo-Δ$^{2(1H),\alpha}$-naphthaleneacetic acid (Isomer B, 11).**—Unsaturated ester **9** (810 mg, 2.5 mmoles) was saponified in the manner just described to give 780 mg of oily product. Crystallization from ether afforded 250 mg of crude **11**, mp 199–205°. Recrystallization from ether gave crystals that melted at 213–215°; λ_{max}^{EtOH} 228 mμ (ε 18,200); nmr (DMSO-d_6), peaks at δ = 0.83–1.2 (6 H, two doublets, methyls) 5.6 and 5.7 ppm (2 H, two singlets, vinyl hydrogens). Recovery of the nmr sample and recrystallization from ether afforded the analytical sample, mp 213–215°.

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.47; H, 7.58; neut equiv, 160.7. Found: C, 67.5; H, 7.5; neut equiv, 163.

Microbiological Oxidation of *dl*-4,4aα,4bβ,5,6,7,8,8aα,9,10-Decahydro-7β-hydroxy-2(3H)-phenanthrone (2).—A suspension of a vegetative growth of *C. bainieri* ATCC 9244 was added to each of ten 500-ml erlenmeyer flasks containing 100 ml of sterile nutrient solution consisting of 5% (w/v) of commercial dextrose (Cerelose), 2% (w/v) of Edamine, and 0.5% (v/v) of cornsteep in tap water. These flasks were incubated in a shaker rotating at 210 cpm with aeration at 26° for 72 hr. The contents of all 10 flasks were then added to 10 l. of the above-described nutrient solution in a 14-l. fermentation tank and the organism was allowed to grow at 27° for 48 hr using an air supply of 4 l./min and agitation at 400 rpm.

A solution of 3.0 g (0.014 mole) of **2** in 15 ml of dimethylformamide was added to each tank under aseptic conditions, and the fermentation was continue for an additional 144 hr. The fermentation was terminated and the broth was adjusted to pH 4.0 by the addition of 6 *N* hydrochloric acid and extracted twice with 10-l. portions of methylene dichloride. The combined organic layers were concentrated under reduced pressure. The residue was washed twice with 250-ml portions of *n*-pentane (to remove lipid material).

The *n*-pentane-washed fermentation extract (43 g) from seven such 3-g runs was dissolved in ethyl acetate and chromatographed on 2 kg of silica gel. The first 8 l. of ethyl acetate eluted brown oils that were discarded. The next 7.5 l. of ethyl acetate gave 4.4 g of a mixture of ***dl*-4,4aα,4bβ,5,6,7,8,8aα,9,10-decahydro-7β,10α-dihydroxy-2(3H)-phenanthrone (12)** and ***dl*-4,4a,4bβ,5,-6,7,8,8aα,9,10-decahydro-4aα,7β-dihydroxy-2(3H)-phenanthrone**

(14) This stock solution was prepared as described by R. V. Oppenauer and H. Oberrauch, *Anales asoc. quím argentina*, **37**, 246 (1949).

(13), with the latter (less polar) being the major constituent. Continued elution with ethyl acetate afforded 6.0 g of oil containing mostly compound 12 (more polar). Each of these fractions was chromatographed on silica gel coated plates (40 × 20 cm) having a 1-mm coating. About 0.25–0.30 g of residue was put on each plate and the plates were developed with ethyl acetate (seven passes were necessary for good separation). The more polar material, crystallizd from acetone containing ether, afforded 1.45 g of the dihydroxy compound (12), mp 143–146°. The analytical sample, obtained from a similar experiment (recrystallized from acetone containing ether), melted at 155–156°; λ_{max}^{EtOH} 237 mμ (ε 14,500).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53. Found: C, 71.0; H, 8.4.

The less polar material, crystallized from acetone with ether added, afforded 1.0 g of the dihydroxy compound (13), mp 151–154°. This same compound, obtained from a similar experiment, was recrystallized further from acetone containing ether to give a sample that melted at 163–165°; λ_{max}^{EtOH} 235 mμ (ε 14,200). This sample was identical by infrared spectral analysis, tlc, melting point, and mixture melting point with a sample produced by the action of *m*-chloroperbenzoic acid on phenanthrol 16 as described below.

***dl*-3,4,4bβ,5,6,7,8,8aα,9,10-Decahydro-7β-hydroxy-2(1H)-phenanthrone (17).**—A solution of 13.8 g (0.06 mole) of phenanthrol 16[2] in 50 ml of tetrahydrofuran was added to 300 ml of liquid ammonia. Lithium wire (4.7 g, 0.66 g-atom) was added in 30 min with stirring. After 30 min more, a mixture of 70 ml of absolute ethanol and 70 ml of absolute ether was added to discharge the blue color. The solution was concentrated to half the volume. Ether and water were added and the layers were separated. The ether was washed with saturated sodium chloride solution and the aqueous layers were washed with a fresh portion of ether. The combined ether layers were dried (Na_2SO_4) and the ether was removed by warming *in vacuo*. The remaining residue was taken up in 100 ml of tetrahydrofuran and 200 ml of methanol. Oxalic acid (10 g) in 75 ml of water was added and the solution was left at room temperature for 75 min at which time it was added to a large volume of ether. The layers were separated and the ether layer was washed several times with saturated sodium bicarbonate solution. The aqueous layers were washed with a fresh portion of ether. The combined ether layers were dried (Na_2SO_4) and the solvent was removed by warming *in vacuo*. The residue crystallized from ether containing hexane and afforded 7.9 g of 17, mp 120–123°. Concentration of the mother liquor afforded 0.4 g of 17, mp 112–117° (yield 63%). The analytical sample, obtained from ether, melted at 125–126°.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.1; H, 9.3.

Oxidation of *dl*-3,4,4bβ,5,6,7,8,8aα,9,10-Decahydro-7β-hydroxy-2(1H)-phenanthrone (17) with *m*-Chloroperbenzoic Acid.—A solution of 6.76 g of 85% *m*-chloroperbenzoic acid (0.032 mole) in 80 ml of methylene dichloride was added to 6.5 g (0.029 mole) of phenanthrone 17 in 50 ml of methylene dichloride. After sitting at room temperature overnight the reaction mixture was washed twice with saturated sodium bicarbonate and once with saturated sodium chloride solution. The aqueous layers were washed again with a fresh portion of methylene dichloride. The organic layers were combined and dried (Na_2SO_4), and the solvent was removed by warming *in vacuo*. An oily residue (6.3 g) remained: λ_{max}^{EtOH} 232 mμ (ε 1300), 278 mμ (ε 80). Tlc indicated that two major components were present. The residue was chromatographed on 500 g of silica gel. Elution with ethyl acetate containing 0.5% of methanol afforded 2.53 g of ***dl*-4,4a,4bβ,5,6,7,8,8aα,9,10-decahydro-4aα,7β-dihydroxy-2(3H)-phenanthrone (13**, 37%, single spot by tlc.) Recrystallization from acetone containing hexane gave the analytical sample (1.43 g): mp 160–161°, λ_{max}^{EtOH} 235 mμ (ε 13,900).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53. Found: C, 70.8; H, 8.3.

Continued elution with the same solvent system afforded 1.74 g of ***dl*-4,4a,4bβ,5,6,7,8,8aα,9,10-decahydro-4aβ,7β-dihydroxy-2(3H)-phenanthrone (18**, 26%, single spot by tlc). Recrystallization from acetone containing hexane gave the analytical sample (0.92 g): mp 176–177°, λ_{max}^{EtOH} 235 mμ (ε 14,500).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53. Found: C, 71.0; H, 8.6.

***dl*-3,4,4a,4bβ,5,6,8,8aα,9,10-Decahydro-4aα-hydroxyphenanthrene-2,7-dione (19).**—A solution of 3 g (0.013 mole) of dihydroxy ketone 13 in 35 ml of pyridine was added to 35 ml of pyridine containing 3 g (0.03 mole) of chromium trioxide. After sitting at room temperature overnight the reaction mixture was added to 500 ml of ethyl acetate. The mixture was then passed through a Supercel cake and the filtrate was warmed *in vacuo* to remove the solvent. The residue was taken up in acetone–ether and more solid was removed by filtration. Upon concentration of the solvent, precipitation of 19 resulted. Filtration afforded 2 g of 19, mp 173–176°. Further concentration gave 0.33 g of 19, mp 166–172° (77%). The analytical sample, obtained from ether, melted at 179–180°.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.76; H, 7.74. Found: C, 71.8; H, 7.5.

***dl*-4bβ,5,6,7,8,8aα,9,10-Octahydro-2,7β-phenanthrenediol 7-Acetate (15).**—A solution of 230 mg (1.0 mmole) of dihydroxy ketone 13 in 17.5 ml of acetic acid and 1.75 ml of 10% sulfuric acid sat under nitrogen for 24 hr. The solution was added to ice–water and solid sodium bicarbonate was carefully added. This mixture was then extracted with ether. The extract was dried (Na_2SO_4) and concentrated to leave 220 mg of an oily residue which was chromatographed on a silica gel coated plate (40 × 20 cm) having a 1-mm coating. The developing solvent was ethyl acetate. The major band was eluted with ethyl acetate to give 120 mg of 15. Recrystallization from ether afforded 100 mg of 15, mp 159–160°.

The analytical sample from ether melted at 160–161°; nmr ($CDCl_3$), peaks at δ = 2.03 (3 H, singlet, acetate methyl), 4.75 (1 H, multiplet, C*H*OAc), 5.90 (1 H, singlet, phenolic OH), and 6.41–7.25 ppm (3 H, multiplet, aromatic).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.83; H, 7.76. Found: C, 73.9; H, 7.9.

***dl*-1,3,4,4aα,4bβ,5,6,7,8,8aα,9,10aβ-Dodecahydro-7β-hydroxyphenanthrene-2,10-dione 7-Acetate (14).**—A solution of 900 mg (3.8 mmoles) of dihydroxy ketone 12 in 50 ml of acetic acid and 5 ml of 10% sulfuric acid sat at room temperature in a nitrogen atmosphere for 24 hr. The solution was poured into ice–water and solid sodium bicarbonate was carefully added. Ether was added, the mixture was shaken, and the layers were separated. The ether was washed with saturated sodium bicarbonate solution and with saturated sodium chloride solution. The aqueous layers were washed with a fresh portion of ether. The combined ether layers were dried (Na_2SO_4) and concentrated by warming *in vacuo* to leave a residue that partially crystallized. A small amount of ether was added to the residue and 310 mg of 14, mp 143–147°, was collected by filtration. The mother liquor was chromatographed on two silica gel coated plates (40 × 20 cm) having a 1-mm coating. The developing solvent was chloroform–ethyl acetate (7:3). Elution of the appropriate band with methanol afforded another 140 mg of 14 (45%). The analytical sample (from ether) melted at 146–148°.

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.06; H, 7.97. Found: C, 69.2; H, 7.8.

Preparation of *cis*- and *trans*-Unsaturated Esters 21 and 20.—A solution of 74 mg (1.37 mmoles) of sodium methoxide in 5 ml of dimethylformamide (DMF) was treated with 248 mg (1.37 mmoles) of trimethyl phosphonoacetate in 5 ml of DMF. The reaction mixture was stirred in an ice bath for 5 min and 160 mg (0.58 mmole) of diketo acetate 14 in 5 ml of DMF was added all at once. The reaction mixture was stirred at room temperature for 45 min and was then added to ice and water. This mixture was made acidic with dilute hydrochloric acid. Sodium chloride was added and the aqueous mixture was extracted with ether. The extract was dried (Na_2SO_4) and concentrated to give a residue (250 mg of oil) that was chromatographed on a silica gel coated plate (40 × 20 cm) having a 1-mm coating. Four passes with an ether–pentane (1:1) solvent system were necessary for proper development. The more polar band from the plate (eluted with methanol) afforded 78 mg (10%) of **methyl *dl*-*cis*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-dodecahydro-7β-hydroxy-10-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate 7-acetate (21)**. Recrystallization from ether afforded 64 mg of 21: mp 131–133°; λ_{max}^{EtOH} 222 mμ (ε 16,900), $\lambda_{max}^{cyclohexane}$ 221 mμ (ε 16,400).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.2; H, 7.7.

The less polar band from the plate (eluted with methanol) afforded 75 mg (40%) of **methyl *dl*-*trans*-3,4,4aα,4bβ,5,6,7,8,8aα,-9,10,10aβ-dodecahydro-7β-hydroxy-10-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate 7-acetate (20)**. Recrystallization from ether afforded 63 mg of 20: mp 145–149°; λ_{max}^{EtOH} 223 mμ (ε 18,400), $\lambda_{max}^{cyclohexane}$ 221 mμ (ε 18,400).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.5; H, 7.5.

dl-trans-**3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-10-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetic Acid (22).**—A solution of 120 mg (0.36 mmole) of methyl unsaturated ester **20** in 20 ml of ethanol and 8 ml of 2 *N* sodium hydroxide was boiled under reflux in a nitrogen atmosphere for 45 min. The reaction mixture was added to ice–water, made acidic with dilute hydrochloric acid, and extracted with ether. The extracts were washed with saturated sodium chloride solution and then dried (Na_2SO_4). The ether was evaporated by warming *in vacuo* to yield 115 mg of a solid residue which was chromatographed on a silica gel coated plate (40 × 20 cm) having a 1-mm coating. This plate was developed with ether–methanol–acetic acid (94:3:3). The appropriate band was eluted with methanol to give 60 mg of **22**, mp 207–212° (60%). Two recrystallizations from acetone gave the analytical sample: mp 237–238° (evacuated tube), λ_{max}^{EtOH} 220 mμ (ε 16,200).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.08; H, 7.97; neut equiv, 278.3. Found: C, 68.9; H, 8.1; neut equiv, 271.

dl-cis-**3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-10-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetic Acid (23).**—In the manner just described, 115 mg (0.35 mmole) of methyl unsaturated ester **21** afforded 55 mg (56%) of **23**, mp 275–276°. Recrystallization from acetone gave the analytical sample: mp 282–283° (evacuated tube), λ_{max}^{EtOH} 220 mμ (ε 15,000).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.08; H, 7.97; neut equiv, 278.3. Found: C, 69.3; H, 8.0; neut equiv, 270.

2-Dimethylaminoethyl *dl-trans*-**3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-10-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate** (*dl*-**15,16,17,20-Tetranorcassaine**) **(24).**—A solution of 270 mg (1.0 mmole) of the *trans* acid **22** in 30 ml of tetrahydrofuran was treated with 52 mg (1.0 mmole) of sodium methoxide. The flask was swirled at room temperature for 5 min and the solvent was removed by warming *in vacuo*. Dry benzene (20 ml) and 0.5 ml of pyridine were added to the residue. The mixture was stirred in an ice bath while 5 ml of oxalyl chloride was added rapidly. The reaction mixture was stirred at room temperature for 5 min. The solvent and excess oxalyl chloride were removed at room temperature *in vacuo*. Dry benzene (20 ml) and 5 ml of dimethylaminoethanol were added. The reaction mixture was heated at 100° for 10 min. Ice and saturated sodium bicarbonate were added and the mixture was extracted with ether. The ether was washed three times with small portions of 2 *N* hydrochloric acid. The acid washes were combined and treated with ice and concentrated sodium hydroxide. The alkaline solution was extracted twice with ether and the extracts were combined, washed with saturated sodium chloride solution, and then dried (Na_2SO_4). Evaporation of the solvent afforded 220 mg of an oily residue which was chromatographed on a silica gel coated plate (40 × 20 cm) having a 1-mm coating. The plate was developed with a chloroform–methanol–isopropylamine (48:1:1) solvent system. The appropriate band was eluted with methanol to afford the oily free base (**24**) which was dissolved in 150 ml of ether and filtered. Ethanolic hydrogen chloride was added to the filtrate until precipitation was complete. The precipitate was collected and recrystallized from acetone to afford 130 mg (35%) of the **hyrochloride**, mp 213–216°. The analytical sample (from acetone) melted at 215–217°; λ_{max}^{EtOH} 226 mμ (ε 18,300).

Anal. Calcd for $C_{20}H_{31}NO_4 \cdot HCl$: C, 62.24; H, 8.36; Cl, 9.19. Found: C, 62.1; H, 8.4; Cl, 9.5.

2-Dimethylaminoethyl *dl-cis*-**3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-10-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (25).**—In the manner just described 85 mg (0.31 mmole) of the *cis* acid **23** afforded 70 mg (60%) of analytically pure **hydrochloride**: mp 224–226°, λ_{max}^{EtOH} 224 mμ (ε 16,200).

Anal. Calcd for $C_{20}H_{31}NO_4 \cdot HCl$: C, 62.24; H, 8.36; Cl, 9.19. Found: C, 62.4; H, 8.6; Cl, 9.4.

Removal of the C-10 Oxygen from Ethyl *dl-cis*-**3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-10-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate 7-Acetate.**—The compound named in the title was prepared from 120 mg of 1,3,4,4aα,4bβ,5,6,7,8,8aα,9,10aβ-dodecahydro-7β-hydroxyphenanthrene-2,10-dione 7-acetate and 306 mg of triethyl phosphonoacetate by the method used to prepare methyl ester **21**. Preparative tlc largely separated the less polar, *cis* isomer (40 mg) (10–15% *trans* isomer remaining) from the *trans* product.

Without characterization, the oily *cis* isomer was dissolved in 0.5 ml of acetic acid and the solution was treated with 0.1 ml of ethanedithiol and 2 drops of boron trifluoride etherate. After 0.5 hr, ice and water were added and the mixture was extracted with ether. The extracts were washed with saturated salt solution, with saturated sodium bicarbonate solution, and again with salt solution. The solvent was removed and the residue was analyzed by silica gel tlc using ether–pentane (1:1) for development. The product showed a single spot which was less polar than the starting material.

The crude thioketal was dissolved in 50 ml of absolute ethanol and 1 teaspoonfull of deactivated Raney nickel (boiled overnight with acetone) was added. This mixture was then heated under reflux for 20 hr, cooled, filtered, and concentrated to a residue.

The crude residue was dissolved in 10 ml of ethanol, 4 ml of 2 *N* sodium hydroxide solution was added, and the solution was refluxed for 0.75 hr. The alcohol was removed by warming *in vacuo* and the residue was partitioned between water and ether. The ether layer was washed once with water and the combined water layers were acidified with 2 *N* hydrochloric acid. The precipitated carboxylic acids were put on a 20 × 20 cm silica gel coated plate which was developed with 3:47:50 acetic acid–ether–pentane. The only ultraviolet-absorbing band present was scraped from the plate and the product was eluted with the developing solvent. Removal of the solvent gave a very small, oily residue which corresponded in R_f with *dl*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-dodecahydro-7β-hydroxy-$\Delta^{2(1H),\alpha}$-phenanthreneacetic acid[3] [*cis–trans* mixture (1:1) of isomers which showed no separation].

This acid was dissolved in approximately 5 ml of methanol and the solution was treated with a tenfold excess of ethereal diazomethane. After standing overnight at room temperature, the solution was concentrated to a residue *in vacuo*. This residual oil (perhaps 1–2 mg) showed the same R_f value as did methyl *dl*-**3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-dodecahydro-7β-hydroxy-$\Delta^{2(1H),\alpha}$-phenanthreneacetate** (prepared from the authentic sample of *cis–trans* acid described in the preceding paragraph by treatment with diazomethane). The product was purified by tlc and then compared with the authentic methyl ester by glpc. The retention times (RT) of the *cis*- and *trans*-methyl esters are 2.86 and 3.09, respectively, relative to 5α-androstane. The methyl ester obtained from desulfurization showed roughly 48% of a material with RT = 2.36 (unknown), 42% with RT = 2.86 (same as known *cis* product), and 10% with RT = 3.09 (same as *trans* product).

Registry No.—**3,** 10232-20-9; **4,** 10232-21-0; **5,** 10232-22-1; **8,** 10232-23-2; **9,** 10232-24-3; **10,** 10232-25-4; **11,** 10232-26-5; **12,** 10232-27-6; **13,** 10232-28-7; **14,** 10232-29-8; **15,** 10232-30-1; **17,** 10232-31-2; **18,** 10232-32-3; **19,** 10232-33-4; **20,** 10232-34-5; **21,** 10232-35-6; **22,** 10232-36-7; **23,** 10232-37-8; **24,** 10232-38-9; **24** hydrochloride, 10232-39-0; **25** hydrochloride, 10232-40-3.

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