group; absorption in dilute HCl, λ_{max} 250–260 mμ (ε 580–1000) (Table III).

Hydrolysis and Deamination of 3-*p*-Chlorophenyl-4,5-dihydro-1-benzazepin-2-one (VIId).—A mixture of 20 g of benzazepinone VIId, 650 ml of concentrated HCl, and 60 ml of AcOH acid was heated under reflux for 4 hr. The solution then was decanted from a small amount of dark oil, diluted with 250 ml of water, and cooled to +5°. The crystalline hydrolysis product was filtered off and dissolved in 2 *N* NaOH. The alkaline solution was acidified carefully to pH 4.5, whereupon the 4-(*o*-aminophenyl)-2-(*p*-chlorophenyl)butyric acid crystallized. It was filtered off and recrystallized from aqueous ethanol (1:1). The yield of product was 15.6 g (73%), mp 150–152°.

Anal. Calcd for $C_{16}H_{16}ClNO_2$: C, 66.3; H, 5.6; N, 4.8. Found: C, 66.5; H, 5.9; N, 5.0.

To a solution of 7 g (0.024 mole) of the above acid in 175 ml of water containing 1 g of NaOH (0.025 mole), there was added 1.72 g (0.025 mole) of $NaNO_2$. This solution was added dropwise with vigorous stirring to a mixture of 12 ml of water and 12 ml of concentrated HCl, the temperature being maintained at approximately 5°. After this addition was completed, stirring of the solution was continued for an additional 20 min at 5°. The diazonium salt solution was then divided into two equal parts. One half was allowed to react with ethanol and $CuSO_4$, the other half was added dropwise to 25 ml of 50% hypophosphorous acid with stirring at 0°. After stirring the latter portion for 2 hr at +5°, the reaction mixture was allowed to stand in the refrigerator for 24 hr. An oil separated, the supernatant solution was decanted, and the oil was dissolved in ether and washed with dilute HCl and then repeatedly with 1 *N* NaOH. Acidification of the NaOH extracts yielded an oil which was taken up in ether, washed with water, and dried. Removal of the ether left 3.1 g of a brown oil which was extracted with four 50-ml portions of boiling hexane. Removal of the hexane *in vacuo* left 1.2 g of a light brown oil which crystallized on seeding. Repeated recrystallization from hexane followed by sublimation gave 4-phenyl-2-*p*-chlorophenylbutyric acid, mp 79–81°, which was identified by mixture melting point with an authentic sample and by thin layer chromatography.

Decomposition of the diazonium salt with ethanol and $CuSO_4$ gave less favorable results than the above described procedure.

Acknowledgments.—The authors wish to thank Dr. W. L. Benoze of the Chemical Research Division for his active participation in this problem, Mr. L. Dorfman, Miss N. Cahoon, and their associates for microanalytical and spectroscopical data, and Dr. A. J. Plummer and Dr. W. E. Barrett of our Division of Macrobiology for the pharmacological data reported in this paper.

Cassaine Analogs. II. 7-Deoxy Basic Esters

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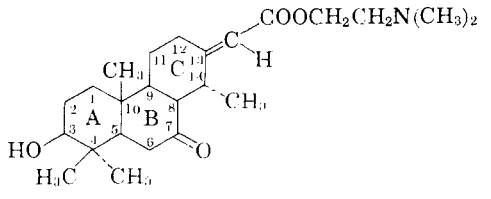
Analogs of the *Erythrophleum* alkaloid cassaine (**1**) have been made in an effort to determine the structural requirements for the cardiotonic effects produced by this alkaloid. None of these has greater cardiotonic activity than that shown by cassaine.

The *Erythrophleum* alkaloid cassaine (**1**) has been recognized for many years as having an intense action on the heart which is quite like that produced by the digitalis glycosides.[1] This rather complex molecule was synthesized recently by Turner, *et al.*[2]



1

With the usual optimism of medicinal chemists, we felt that perhaps the complications of having an oxygen function at C-7 and methyl groups at C-4, -10, and -14 might not be necessary for cardiotonic activity and that a modified cassaine, carrying substituents only at C-3 and C-13, might be a useful cardiac drug. The present paper describes the preparation and biological testing of several such simplified analogs together with compounds in which the C-4, -10, and -14 methyl groups have been in part replaced.

The general synthetic reaction utilized in preparing the requisite α,β-unsaturated basic esters is illustrated in Scheme I. Triethyl phosphonoacetate reacted with tricyclic hydroxy ketone **2** to form a 1:1 mixture of esters **3** and **5** which are isomeric about the double bond.[3] This mixture was not separable in our hands by thin layer chromatography (tlc) but its composition was demonstrable by gas–liquid partition chromatography (glpc). The *trans* structure (present in **3**) is defined as that in which the carboxyl group lies away from the bulge of the B ring.

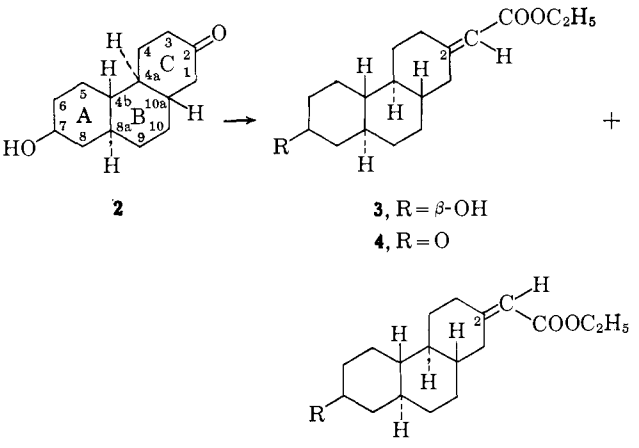
In the present work the *trans* structure is assigned to that isomer of each pair having the longer glpc retention time. It is perhaps significant that in four of the five cases presently reported where pairs of isomers have been actually separated, the *trans* isomer has a significantly greater ultraviolet extinction coefficient than does its *cis* counterpart. In the sixth case the coefficients were about equal. The cause of such differences

(1) See F. Erjavec and Š. Adamič, *Arch. Intern. Pharmacodyn.*, **155**, 251 (1965); E. L. McCawley, *Alkaloids*, **5**, 101 (1955), and references therein.

(2) R. B. Turner, O. Buchardt, E. Herzog, R. B. Morin, A. Riehl, and J. M. Sanders, *J. Am. Chem. Soc.*, **88**, 1766 (1966).

(3) In the large number of Wittig reactions reported here, we found no evidence of any stereospecificity in formation of the *trans vs.* the *cis* unsaturated esters with the exception of the case where an equatorial methyl group was present at C-1 (phenanthrene numbering). Here there appeared to be a preponderance of the *trans* isomer. A. K. Bose and R. T. Dahill, *J. Org. Chem.*, **30**, 505 (1965), report obtaining essentially a single isomer from the reaction of triethyl phosphonoacetate with 3-keto steroids and H. Kaneko and M. Okazaki, *Tetrahedron Letters*, 219 (1966), found that the isomer ratio in this reaction could be varied by choice of reaction conditions. These steroids differ from the presently reported compounds in having an axial methyl group "*para*" to the ketone undergoing reaction which might effect some stereochemical direction in the reaction.

SCHEME I



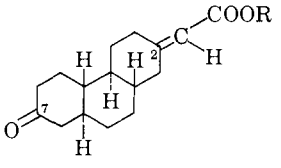
2

3, R = β-OH
4, R = O

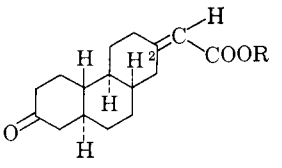
5, R = β-OH
6, R = O

is not immediately evident since no influencing structures seem to lie near the chromophore. A discussion of this configurational assignment together with that in the C-10 oxo series and the cassaine series is given in the paper devoted to 10-oxophenanthreneacetic acid derivatives.[4]

Oxidation of the mixture of **3** and **5** with CrO_3 in pyridine afforded a mixture of ketones from which the *trans* isomer (**4**) could be obtained essentially pure by crystallization. It was then hydrolyzed to give the pure *trans* acid (**7**). The mother liquor from separation of the *trans* ester (**4**) was rich in *cis* ester (**6**) and hydrolysis of this mixture allowed separation of the *cis* acid (**9**). Esterification of the mother liquor from **9** with diazomethane furnished more of the *cis* isomer



7, R = H
8, R = $CH_2CH_2N(CH_3)_2$

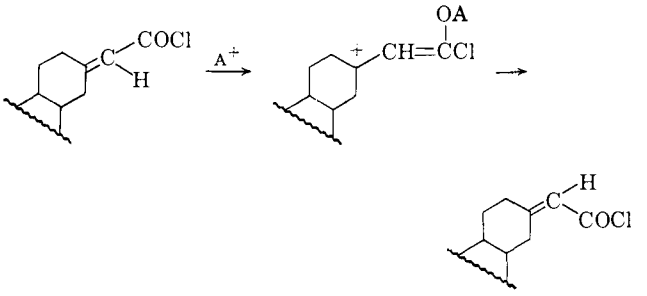


9, R = H
10, R = CH_3
11, R = $CH_2CH_2N(CH_3)_2$

as its methyl ester (**10**) and hydrolysis of **10** afforded the purest sample of *cis* acid **9** obtained in this work.

Treatment of the sodium salts of isomers **7** and **9** with oxalyl chloride followed by dimethylaminoethanol produced *trans* (**8**) and *cis* (**11**) basic esters which formed nicely crystalline, water-soluble hydrochloride salts. The reaction of the sodium salts with oxalyl chloride is essentially complete within 5–10 min at room temperature. When a single isomer is at hand, it is necessary at this point to remove excess oxalyl chloride and to add the required amino alcohol as quickly as possible since allowance of the acid chloride to stand at room temperature for an extended period or heating it briefly with steam following solvent removal causes isomerization and production of a *cis–trans* mixture. The Experimental Section records an instance of complete equilibration of a *trans* acid (compound J, Table II) to a **1**:**1** mixture of *cis* and *trans* basic esters (compound J, Table III). Although the mechanism of this isomerization is not proven, it probably involves carbonium ion formation under the influence of acid (Scheme II).

SCHEME II



Since the present work was directed toward determining the relationship between structure and activity, it was necessary to separate the *cis* and *trans* isomers in only a few confirmatory instances because the difference in cardiotonic activity of these isomers was minor. The principal inconvenience in working with such isomer mixtures lay in their broad melting points.

An exceptionally useful technique for purifying many of the basic esters reported here was that described by Brown and Kupchan[5] which involves partition chromatography of basic materials. A dye which is incorporated in the stationary phase indicates the degree of movement and separation of the bases on the column. This method did not, however, effect separation of our *cis* and *trans* isomers.

Tables I–III summarize most of the alkyl esters (Wittig products), carboxylic acids, and basic esters presently reported and footnotes to these tables describe deviations from the standard procedures given in the Experimental Section. Unless otherwise noted, the reaction sequence involved ketone → alkyl ester → acid → basic ester. The tricyclic ketones used in the preparation of the esters of Table I are described by Daum, *et al.*,[6] with the exception of the ketone precursors of compounds A and O of Table I which are described in the Experimental Section.

Examination of Table III reveals the general scope of the investigation. Compound A has no oxygen function in either rings A or B. Compounds B–F and I have the same side chain at C-2 (phenanthrene numbering) but differ at C-7. Compounds G, H, and J–Q fall into this same category except that they carry a C-4b methyl group. Compounds R–Z differ principally in the type of side chain at C-2. The amide Z is the only nonester listed. It should be noted that compound F contains a Δ^8 bond, compound AA has an additional methyl group at C-1, compound BB has two methyl groups at C-8, compounds CC and DD have rings A and B fused in a *cis* manner and, finally, that EE has rings B and C fused in a *cis* manner. Several additional basic esters are described later owing to their special mode of synthesis.

Isolation of the primary aminoethyl ester W of Table III was difficult on account of the propensity for such esters to rearrange to β-hydroxyamides.[7] This

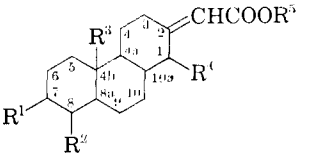
(4) S. J. Daum, M. M. Riano, P. E. Shaw, and R. L. Clarke, *J. Org. Chem.*, **32** 1435 (1967).

(5) K. S. Brown and S. M. Kupchan, *J. Chromatog.*, **9**, 71 (1962).

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

(7) See G. Fodor, *Acta Chim. Acad. Sci. Hung.*, **5**, 379 (1954), and especially p 389.

TABLE I
TRICYCLIC α,β-UNSATURATED ALKYL ESTERS



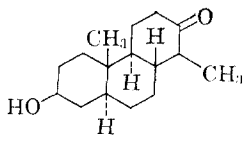
Compd	R^1	R^2	R^3	R^4	R^5	*trans*:*cis* Ratio	Mp, °C	Ultraviolet[a] λ, mμ	ε	Yield, %	Formula	Found,[b] % C	H
A[c]	H	H	CH_3	H	CH_3	1:1	Oil[d]	224	16,000	81	$C_{18}H_{28}O_2$		
B[c,e]	β-OH	H	H	H	C_2H_5	1:1	102–110	223	17,500	95	$C_{18}H_{28}O_3$	74.2	9.9
C[c]	β-OH	H	H	H	CH_3	1:1	Oil				$C_{17}H_{26}O_3$		
D[f]	O=	H	H	H	C_2H_5	*trans*	95–96.5[g]	223	18,300	26	$C_{18}H_{26}O_3$	74.7	9.2
E[f]	O=	H	H	H	CH_3	*cis*	139–141[h]	223	17,100		$C_{17}H_{24}O_3$	74.0	8.8
F[i]	α-OH	H	H	H	C_2H_5	1:1	Oil				$C_{18}H_{28}O_3$		
G[c]	O=	Δ[b]	H	H	CH_3	1:1	Oil	235	27,500		$C_{17}H_{22}O_3$		
H[c]	CH_2S / CH_2S	H	H	H	CH_3	1:1	Oil				$C_{19}H_{28}O_2S_2$		
I[c]	β-OH	H	CH_3	H	CH_3	1:1	Oil				$C_{18}H_{28}O_3$		
J[c]	O=	H	CH_3	H	CH_3	1:1	Oil				$C_{18}H_{26}O_3$		
K[c]	β-OH	H	CH_3	H	C_2H_5	1:1	Oil				$C_{19}H_{30}O_3$		
L[j]	O=	H	CH_3	H	C_2H_5	6:1					$C_{19}H_{28}O_3$		
M[f]	O=	H	CH_3	H	C_2H_5	1:6					$C_{19}H_{28}O_3$		
N[f]	β-OH	H	CH_3	CH_3	CH_3	7:3	Oil				$C_{19}H_{30}O_3$		
O[c]	β-OH	$(CH_3)_2$	CH_3	H	CH_3	1:1	Oil				$C_{20}H_{32}O_3$		
P[c,i]	α-OH	H	H	H	C_2H_5	1:1	Oil				$C_{18}H_{28}O_3$		
Q[c,i]	O=	H	H	H	C_2H_5	1:1	Oil				$C_{18}H_{26}O_3$		
R[c,k]	β-OH	H	H	H	CH_3	1:1	Oil				$C_{17}H_{26}O_3$		
S[l]	O=	Δ[8]	β-OH	H	CH_3	1:1	162–196[h]	229	28,100	74	$C_{17}H_{22}O_3$	70.6	7.6

[a] Measured in 95% ethanol. [b] All found values are within 0.3% of calculated values. [c] Ketone precursor described in Experimental Section. [d] Tlc showed single spot. [e] Ketone precursor described in ref 6. [f] This preparation is described in detail in the Experimental Section. [g] Recrystallized from ether–hexane. [h] Recrystallized from ether. [i] Prepared by oxidation of compound immediately above in this table using method to prepare text compound **4**; see Experimental Section. [j] Rings A and B are fused in a *cis* manner (4bβ, 8aβ). [k] Rings B and C are fused in a *cis* manner (4aα, 10aα). [l] Ketone precursor described in ref 4.

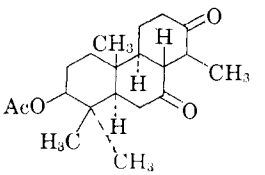
amino group was protected through its carbobenzoxy derivative during ester formation and the resulting ester (V, Table III) was readily cleaved with trifluoroacetic acid in 24 hr at room temperature. No rearrangement occured under these acidic conditions. It proved possible to streak this aminoethyl ester–trifluoroacetate salt on silica-coated preparative chromatoplates, develop and elute quickly with tetrahydrofuran (THF) containing isopropylamine, and convert the purified aminoester to its stable hydrochloride salt without serious decomposition.

Surprisingly, it is possible to convert 7-hydroxy unsaturated acids such as D, N, O, and S of Table II directly to 7-hydroxy basic esters by the oxalyl chloride technique. Almost certainly an oxalyl ester–acid chloride forms at C-7 but treatment of this intermediate with dimethylaminoethanol in boiling benzene (usual treatment in side-chain ester formation) results in regeneration of the free hydroxyl group at C-7.

Whereas the Wittig reaction producing the esters of Table I normally proceeds rapidly with negligible starting material demonstrable in the crude products by tlc, reaction of trimethylphosphonoacetate with ketone **12** always resulted in recovery of about 50% of unchanged starting material. This recovered material then underwent a further 50% conversion under the same conditions. Extending the reaction time, elevating the temperature, or increasing the proportion of Wittig reagent present failed to produce further reaction. It is possible that an equatorial methyl group adjacent to the carbonyl group causes formation of an enol phosphate as a competing product which regenerates starting material during work-up. Periodic check of the reaction mixture on silica tlc plates always showed a spot representing this unchanged starting material. The same partial Wittig reaction was observed when an equatorial methyl group was present in a precursor (**13**) to methyl 14-epicassaiate but not when this methyl group was axial.[8] By analogy with the Wittig reaction on **13**, the predominant component (70%) of the product from the reaction with **12** was assigned the *trans*-equatorial structure. The minor product could well have been other than the *cis*-equatorial form.[8]



12



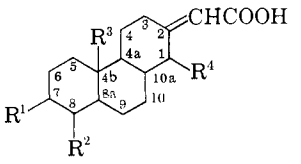
13

A first attempt to prepare ester **14** by a Wittig reaction between triethyl α-phosphonopropionate **16** and the requisite tricyclic ketone failed completely when dimethoxyethane was used as a solvent, even with a reflux period of 3 days. With dimethyl sulfoxide as the solvent,[9] **14** was isolated in 71% yield. Hydrolysis and esterification with 2-dimethylaminoethanol con-

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

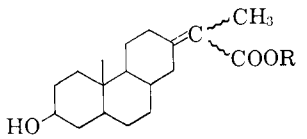
(9) The usefulness of this solvent in Wittig reactions has been observed by R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

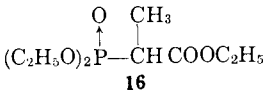
TABLE II
TRICYCLIC α,β-UNSATURATED ACIDS



Compd	R^1	R^2	R^3	R^4	*trans*:*cis* ratio	Mp, °C	Ultraviolet[a] λ, mμ	ε	Yield, %	Formula	Found,[b] % C	H	S
A	H	H	CH_3	H	1:1	169–179[c]	222	15,800	75	$C_{17}H_{26}O_2$	77.7	10.1	
B[d]	O=	H	H	H	*cis*	220–222[c,e]	221	15,400	80	$C_{16}H_{22}O_3$	73.1	8.4	
C[d]	O=	H	H	H	*trans*	224–227[c,e]	222	16,200	78	$C_{16}H_{22}O_3$	73.5	8.4	
D	α-OH	H	H	H	1:1	173–189[c]	223	15,400	80[f]	$C_{16}H_{24}O_3$	72.6	9.1	
E[g]	β-OH	H	H	H	1:1	205–207[c]			54[f]	$C_{16}H_{24}O_3$	72.8	9.2	
F	O=	Δ[8]	H	H	1:1	194–200[c]	235	25,800	54	$C_{16}H_{20}O_3$	74.2	7.8	
G[d]	CH_2S / CH_2S	H	CH_3	H	...	254–259[h]	221	16,600	75	$C_{19}H_{28}O_2S_2$	353[i]		18.0
H[j]	CH_2S / CH_2S	H	H	H	1:1	187–220[k]	219	16,900	57[f]	$C_{18}H_{26}O_2S_2$	64.3[l]	8.0	19.0
I[d]	CH_2SO_2 / CH_2SO_2	H	H	H	...	270–271[k]	221	16,700	92	$C_{18}H_{26}O_6S_2$	54.0	6.7	15.8
J[m]	O=	H	CH_3	H	...	194–200[c]	221	16,400	25[n]	$C_{17}H_{24}O_3$	73.9	8.8	
K[o]	O=	H	CH_3	H	*trans*	181–184[c]	221	16,200	66	$C_{17}H_{24}O_3$	73.8	8.7	
L[p]	O=	H	CH_3	H	*cis*	219–221[c]	221	16,100	40	$C_{17}H_{24}O_3$	74.1	8.7	
M[d]	CH_2CH_2 / CH_2CH_2 >N	H	CH_3	H	...	Used crude				$C_{21}H_{32}NO_2$			
N[q]	β-OH	H	CH_3	H	1:1	173–212[r]	222	16,000	75	$C_{17}H_{26}O_3$	73.0	9.3	
O[s]	β-OH	H	CH_3	H	*trans*	223–225[s]	221	16,100		$C_{17}H_{26}O_3$	73.7[l]	9.6	
P[t]	β-OH	H	CH_3	H	*cis*	198–200[u]	222	15,300	48	$C_{17}H_{26}O_3$	73.3	9.5	
Q	β-OH	H	CH_3	CH_3	...	Used crude				$C_{18}H_{28}O_3$			
R	β-OH	$(CH_3)_2$	CH_3	H	1:1	186–190[k]	222	16,500	43[f]	$C_{19}H_{30}O_3$	74.8	10.0	
S[v]	O=	H	H	H	1:1	185–200[c]	222	16,000	72	$C_{16}H_{22}O_3$	72.8[w]	8.4	
T[x]	β-OH	H	H	H	1:1	Used crude				$C_{16}H_{24}O_3$			
U	O=	Δ[8]	β-OH	H	1:1	208–232[k]	229	24,500	61	$C_{16}H_{20}O_4$	*y*	7.1	

[a] Measured in 95% ethanol. [b] All analytical values are within 0.3% of those calculated unless otherwise noted. [c] From ethyl acetate. [d] This preparation is described in detail in the Experimental Section. [e] In an evacuated capillary. [f] Yield for two steps from tricyclic ketone. [g] Prepared from C of Table I. [h] From acetic acid. [i] Neutralization equivalent (calcd 352.5). [j] Product purified by chromatography on silica gel coated plates with development by 3:47:50 acetic acid–pentane–ether. [k] From acetone. [l] Analytical value 0.4% high. [m] Prepared from J of Table I. [n] Yield for three steps from tricyclic ketone through I and then J of Table I. [o] From L of Table I. [p] From M of Table I. [q] From I of Table I. [r] From acetone–hexane. [s] From N of this table by recrystallization three times from acetone and once from acetonitrile. [t] Prepared from basic ester M, Table III, by alkaline hydrolysis in the standard manner. [u] From ether. [v] Rings A and B are fused in a *cis* manner (4bβ, 8aβ). [w] Analytical value 0.5% low. [x] Rings B and C are fused in a *cis* manner (4aα, 10aα). [y] Analytical results were erratic over several per cent. Tlc showed a single spot. Compounds gave the corresponding basic ester which showed correct analysis.



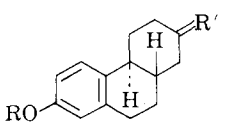


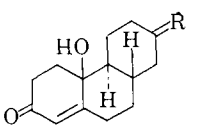
16

14, R = C_2H_5
15, R = $CH_2CH_2N(CH_3)_2$

verted ester **14** to basic ester **15** as a mixture of *cis* and *trans* isomers.

An analog of the above basic esters wherein ring A was aromatic (**18**) was prepared in the standard manner by a Wittig reaction on ketone **17** followed by hydrolysis and esterification with dimethylaminoethanol. The related phenolic ester **19** came from an unexpected direction. Ketone **20**[4] was converted through Wittig product **21** to a C-4b hydroxylated acid **22** with the intent to prepare the corresponding dimethylaminoethyl ester. In the process of treating the sodium salt of acid **22** with oxalyl chloride and dimethylaminoethanol, elimination of the hydroxyl group occurred with aromatization of ring A and formation of the phenolic basic ester **19**.

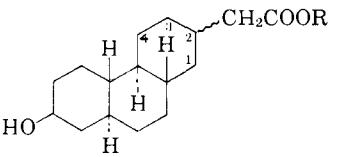




17, R = CH_3; R′ = O
18, R = CH_3; R′ = $CHCOOCH_2CH_2N(CH_3)_2$
19, R = H; R′ = $CHCOOCH_2CH_2N(CH_3)_2$

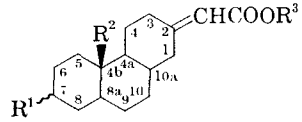
20, R = O
21, R = $CHCOOCH_3$
22, R = CHCOOH

Hydrogenation of unsaturated ester **3** in the presence of Pd–C produced a mixture of compounds **23a** which were epimeric at C-2. These were simply designated isomers A and B in the absence of a basis for configurational assignment. Isomer A crystallized spontaneously from the mixture. Hydrolysis of the mother liquor afforded isomer B in the form of its acid **23b**. The corresponding pure isomeric basic esters A and B, **23c**, were then readily prepared through their acid chlorides. Neither the isomers of **23a** nor those of **23c**



23a, R = C_2H_5
b, R = H
c, R = $CH_2CH_2N(CH_3)_2$

TABLE III
TRICYCLIC α,β-UNSATURATED BASIC ESTERS



Compd	R¹	R²	R³	*trans*:*cis* ratio	Mp, °C	Ultraviolet[a] λ, mμ	ε	Yield, %	Formula	Found,[b] % C	H	N
A	H	CH_3	$CH_2CH_2N(CH_3)_2$	1:1	192–198[c,d]	228	17,300	57	$C_{21}H_{35}NO_2\cdot HCl$	68.2	9.5	9.7[e]
B	O=	H	$CH_2CH_2N(CH_3)_2$	*trans*	181–183.5[e,f]	227	18,300	56	$C_{20}H_{31}NO_3\cdot HCl$	65.0	8.6	3.6
C	O=	H	$CH_2CH_2N(CH_3)_2$	*cis*	174.5–175.5[e,f,g]	226	17,400	33	$C_{20}H_{31}NO_3\cdot HCl$	64.3	8.7	9.4[e]
D[h]	O=	H	$CH_2CH_2N(CH_3)_2$	1:1	156–162[e,i]	226	18,600	46	$C_{20}H_{31}NO_3\cdot HCl$	64.7	8.6	9.6[e]
E	α-OH	H	$CH_2CH_2N(CH_3)_2$	1:1	167–160[f,i]	227	17,500	68	$C_{20}H_{33}NO_3\cdot CH_3SO_3H$	58.6	8.6	7.6[j]
F[k]	O=	H	$CH_2CH_2N(CH_3)_2$	1:1	149–188[e,l]	235	29,600	28	$C_{20}H_{29}NO_3\cdot HCl$	64.9[m]	8.4	9.9[e]
G[n]	CH_2S / CH_2S	CH_3	$CH_2CH_2N(CH_3)_2$	9:1	116–120[f,o]			52	$C_{23}H_{37}NO_2S_2$		15.2[j]	
				...	230–232[e,p]				$C_{23}H_{37}NO_2S_2\cdot HCl$		14.0[j]	7.7[e]
H[q]	$NH_2C(=NH)NHN=$	CH_3	$CH_2CH_2N(CH_3)_2$	1:1	167 dec[e,r]	228	30,500	77	$C_{22}H_{37}N_5O_2\cdot 2HCl$	55.3	8.3	14.4
I[s]	CH_2SO_2 / CH_2SO_2	H	$CH_2CH_2N(CH_3)_2$	1:1	255–260[e,f]	225	17,800	46	$C_{22}H_{35}NO_6S_2\cdot HCl$	51.6	7.3	12.5[t]
J[k]	O=	CH_3	$CH_2CH_2N(CH_3)_2$	1:1	146–148[e,l]	226	18,700	73	$C_{21}H_{33}NO_3\cdot CH_3SO_3H$	59.7	8.4	7.2[j]
K[t]	β-OH	CH_3	$CH_2CH_2N(CH_3)_2$	4:6	218–236[e,d]	227	17,700	58	$C_{21}H_{35}NO_3\cdot HCl$	65.1	9.4	9.1[e]
L[u]	β-OH	CH_3	$CH_2CH_2N(CH_3)_2$	*trans*	238–241[d,i,v]	228	18,600		$C_{21}H_{35}NO_3\cdot CH_3SO_3H$	59.4	8.7	7.2[j]
M[u]	β-OH	CH_3	$CH_2CH_2N(CH_3)_2$	*cis*	222–224[d,i,w]	228	17,700		$C_{21}H_{35}NO_3\cdot CH_3SO_3H$	59.2	8.8	7.2[j]
N[q]	β-OAc	CH_3	$CH_2CH_2N(CH_3)_2$	*trans*	184–188[e,l]	227	18,700	91	$C_{23}H_{37}NO_4\cdot HCl$	64.7	9.1	8.4[e]
O[q]	β-OBz	CH_3	$CH_2CH_2N(CH_3)_2$		226–230[e,d]	229[x]	32,800		$C_{28}H_{39}NO_4\cdot HCl$	68.6	8.5	7.3[e]
P[q]	O_2NO—	CH_3	$CH_2CH_2N(CH_3)_2$	1:1	180–181[e,r,v]			74	$C_{21}H_{34}N_2O_5\cdot HCl$	58.7	8.5	6.8
Q[s]	CH_2CH_2 / CH_2CH_2 >N	CH_3	$CH_2CH_2N(CH_3)_2$	1:1	280 dec[e,d,g,w]			43	$C_{25}H_{42}N_2O_2\cdot 2HCl$	62.5	9.4	14.8[e]
R	O=	H	$(CH_2)_3N(CH_3)_2$	1:3	158–165[f,i]	224	18,100	33	$C_{21}H_{33}NO_3\cdot CH_3SO_3H$	59.3	8.5	7.3[j]
S	β-OH	H	$(CH_2)_3N(CH_3)_2$		176–184[e,f]	225	17,100	50	$C_{21}H_{35}NO_3\cdot HCl$	65.5	9.5	9.3[e]
T	O=	CH_3	$(CH_2)_4N(CH_3)_2$	1.4:1	130–138[e,i]	223	17,300	25	$C_{23}H_{37}NO_3\cdot HCl$	67.0	9.1	8.8[e]
U[y]	β-OH	CH_3	$CH(CH_3)CH_2N(CH_3)_2$	1:1	202–208[d,i]	228	17,600	24	$C_{22}H_{37}NO_3\cdot CH_3SO_3H$	59.9	8.8	6.9[j]
V[u]	O=	CH_3	$CH_2CH_2NH_2$		258–259[e]			40	$C_{19}H_{29}NO_3\cdot HCl$	64.4	8.4	10.1[e]
W	β-OH	H	$CH_2CH_2N(C_2H_5)_2$	1:1	147–155[e,r]	226	16,600	41	$C_{22}H_{37}NO_3\cdot HCl$	65.9	9.7	9.0[e]
X[s]	β-OH	H	$CH_2CH_2N(i\text{-}C_3H_7)_2$	1.5:1	183–185[e,f]	227	18,800	37	$C_{24}H_{41}NO_3\cdot HCl$	67.4	10.0	8.5[e]
Y	O=	H	$CHCH_3CH_2N(CH_3)CH_2CH_2$	1:1.4	155–170[e,l,v]	226	18,500		$C_{22}H_{33}NO_3\cdot HCl$	66.4	8.6	3.5
Z[p,aa]	O=	H	$NHCH_2CH_2N(CH_3)_2$[aa]	1:1	137–165[i,z]	225	20,900	39	$C_{20}H_{32}N_2O_2\cdot CH_3SO_3H$	58.9	8.5	6.2[m]
AA[bb]	β-OH	CH_3	$CH_2CH_2N(CH_3)_2$	19:1	239–242[e,d]	228	17,200	36	$C_{22}H_{37}NO_3\cdot HCl$	66.3	9.3	8.9[e]
BB[cc]	β-OH	CH_3	$CH_2CH_2N(CH_3)_2$		202–224[e,f]	228	18,200	50	$C_{23}H_{39}NO_3\cdot HCl$	66.5	9.5	3.2
CC[a,dd]	O=	H	$CH_2CH_2N(CH_3)_2$	1:3	181–188[e,f]	226	18,400	33	$C_{20}H_{31}NO_3\cdot HCl$	65.2	9.0	3.9
DD[t,dd]	α-OH	H	$CH_2CH_2N(CH_3)_2$	9:1	194–195[e,f]				$C_{20}H_{33}NO_3\cdot HCl$	64.7	9.5	4.0
EE[ee]	β-OH	H	$CH_2CH_2N(CH_3)_2$	1:1	184–202[i,z]	222	18,400	59	$C_{20}H_{33}NO_3\cdot CH_3SO_3H$	58.2	8.6	7.4[t]

[a] Measured in 95% ethanol. [b] All found values are within 0.3% of the calculated values unless a note indicates otherwise. [c] Hydrochloride salt. [d] Recrystallized from acetonitrile. [e] Chlorine analysis. [f] Recrystallized from acetone. [g] Contains 0.25 mole of H_2O. *Anal.* Calcd: H_2O, 1.20. Found: H_2O, 1.21. [h] Prepared by standard procedure but chromatography was not required. [i] Methanesulfonate salt. [j] Sulfur analysis. [k] Contains Δ^8 bond. [l] Recrystallized from ethyl acetate. [m] Value off by 0.4%. [n] Purified on silica gel coated chromatoplates developed with 1.5:1.5:97 methanol–isopropylamine–$CHCl_3$ instead of by partition chromatography. [o] Free base. [p] Dissolved in methanol and precipitated by ether and pentane. [q] Preparation described in Experimental Section. [r] Dissolved in methanol and precipitated with ether. [s] Purified as by footnote *n* except for using a 3:3:94 solvent mixture. [t] Prepared by reduction with $NaBH_4$. See Experimental Section. [u] Isomer separated by fractional crystallization. See Experimental Section. [v] Melts with decomposition. [w] In an evacuated capillary. [x] Also 272 and 280 mμ with ε 1100 and 800, respectively. [y] Prepared normally except that 2-dimethylaminopropanol was used. [z] From acetone with ether added. [aa] This compound is an amide of structure =CHCONH-$CH_2CH_2N(CH_3)_2$. [bb] This compound has a β-CH_3 group on C-1. [cc] This compound has two CH_3 groups on C-8. [dd] Rings A and B are fused in a *cis* manner (4bβ, 8aβ). [ee] Rings B and C are fused in a *cis* manner (4aα, 10aα).

could be separated by tlc but those of **23b** were separable, isomer B being the more polar.

Biological Methods

The initial test for cardiotonic activity was performed in the isolated appendage of the rabbit heart. A more advanced evaluation of drug action was made in the dog.

Rabbit.—Appendages were suspended in Tyrode solution at 37° and stimulated by rectangular pulses (supramaximal voltage, 180/min, 10 msec duration) *via* Pt electrodes. After 75 min the tyrode solution was replaced with fresh solution and 15 min later drugs were added. The sequence of drug concentrations (expressed in terms of the base) was 0.01, 0.05, 0.1, 0.5, 1, 5, and 10 μg/ml with a 10-min interval between each concentration change. Contractile force was recorded isometrically on a Grass polygraph by means of a force-displacement transducer.

Dog.—Cardiovascular activity in anesthetized (pentobarbital, 30 mg/kg iv) spontaneously respiring dogs was recorded on a Grass polygraph. Blood pressure in the abdominal aorta was measured by means of a Statham pressure transducer *via* a polyethylene cannula inserted into the femoral artery. Heart contractile force was measured isometrically by means of a Walton–Brodie strain gauge arch sutured to the wall of the right ventricle.[10] Heart rate was calculated from the force recordings and cardiac electrical activity was monitored *via* a lead II electrocardiogram. Drugs as salts were dissolved in distilled water and administered into the femoral vein usually in the sequence 0.25, 0.5, 1, 2, and 4 mg (calculated as free base)/kg of body weight. Dose–response curves were fitted to the data by eye and the dose producing a 20% increase in contractile force was estimated from the regression of the curve. Cumulative doses were used in constructing the dose–response curve of ouabain. In the infusion experiments a constant-speed infusion pump was used to deliver the drugs to anesthetized animals (pentobarbital, 30 mg/kg iv; α-chloralose, 80 mg/kg iv).

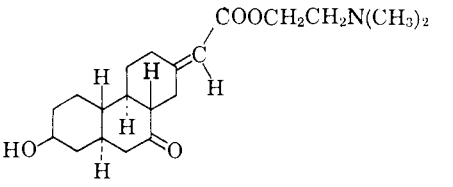
Results

Table IV presents the testing results in both the isolated appendage of the rabbit heart and in the intact dog. Discussion of cardiotonic activity relative to the structural modification of the cassaine molecule can be conveniently divided into two parts: (1) that dealing with alterations in the phenanthrene nucleus, and (2) that concerning changes in the side chain at C-2.

Changes in the Phenanthrene Nucleus.—The results show that the substituent at C-3 [cassaine (**1**) numbering] can greatly influence the cardiotonic activity of the mole. The most active compounds contained an ethylenedisulfonyl group (I) and an amidinohydrazone group (H) at this position. Compounds containing 3α- or 3β-hydroxyl groups were about equiactive (E and K). Furthermore, the substitution of a carbonyl group (D and J) for a hydroxy group (E) did not affect activity. However, replacement of the hydroxyl by a hydrogen atom resulted in a less active compound (A).

No significant change in cardiotonic activity was observed upon addition of two methyl groups at C-4 (BB), an equatorial methyl group at C-14 (AA), or an axial methyl group at C-10 (compare D and J). It should be noted that cassaine carries an axial methyl group at C-14.

The preparation of **24** is described in ref 4. This "ring-demethylated" cassaine seems to be even less active than the cassaine analogs without a ring-B oxygen (see Table IV, **24**).



24

The manner of fusion of the A/B and B/C rings does not greatly alter cardiotonic activity. Compounds CC and DD, having an A/B *cis* fusion, are slightly less active than compound EE which has rings B and C fused in a *cis* manner.

Changes in the Side Chain.—The question of relative activity when the side chain is in the *cis vs. trans* configuration was answered by comparing compounds B with C and L with M. In both instances there is no major difference in activity. A mixture of B and C is represented by D and a mixture of L and M (4:6) is present as K.

Hydrogenation of the double bond of the side chain (**23**) caused a diminution in cardiotonic activity. Decreased activity was also noted with the substitution of a methyl group on the double-bonded C atom of the side chain (**15**). Replacement of the ester linkage by an amide (Z) resulted in a compound which depressed contractile force. Elongation of the alcohol portion of the side chain from dimethylaminoethyl to dimethylaminobutyl (T) had no effect on cardiotonic activity.

The effect of the size of the substituents on the amino nitrogen was significant. Hydrogen atoms (V) could be substituted for methyl groups (J) with no loss of activity. However, the diethyl analog (W) was only weakly active and the isopropyl analog (X) depressed contractile force in the dog ventricle.

Toxicity.—Table IV shows that low concentrations of the synthetic cassaine analogs possess positive inotropic activity in the isolated rabbit appendage. As the concentration of drug in the bath was increased, toxic effects were observed, *i.e.*, arrhythmic beating, a negative inotropic action, and cessation of beating. These effects were also observed with ouabain and cassaine (see Table IV) and are typical of the cardiac glycosides. A similar sequence of effects was observed after intravenous administration of single doses of the synthetic compounds to the intact anesthetized dog (Table IV). Low doses produced an increase in ventricular contractile force, intermediate doses resulted in cardiac slowing, and high doses evoked toxic effects, *i.e.*, A–V block, ventricular ectopic beats, ventricular fibrillation, and respiratory arrest.

The results of experiments in which L and cassaine were *infused* into the femoral vein of the dog are summarized in Table V. Tremors were observed after 15 min in only 1/3 dogs anesthetized with pentobarbital, whereas clonic–tonic convulsions were observed after 4 and 6 min in 2/3 dogs anesthetized with α-chloralose. The third dog in the latter group exhibited severe tremors after 15 min. It would, therefore, appear that convulsive activity due to the synthetic compound is readily suppressed by prior administration of barbiturates (but not by α-chloralose), a characteristic shared by cassaine.[11]

(10) T. G. Brown, Jr., and A. M. Lands in "The Evaluation of Drug Activity," Vol. 1, D. R. Lawrence and A. L. Bacharach, Ed., Academic Press Inc., New York, N. Y., 1964, Chapter 17.

(11) M. deV. Cotten, L. I. Goldberg, and R. P. Walton, *J. Pharmacol. Exptl. Therap.*, **106**, 94 (1952).

TABLE IV
CARDIOTONIC ACTION AND TOXICITY OF CASSAINE ANALOGS IN THE ISOLATED RABBIT APPENDAGE AND IN THE INTACT ANESTHETIZED DOG VENTRICLE

	Rabbit				Dog	
		Comen producing				
Compd	No. of expts	(+)-Inotropic effect,[a] μg/ml[b]	Arrhythmias or conduction block, μg/ml[b]	(−)-Inotropic effect, μg/ml[b]	No. of expts	Dose (iv) producing a 20% ↑ in contractile force, mg/kg[c]	Mortality at high doses, mg/kg
Ouabain	4	0.01–0.1	0.5–1	1	16	0.03	
Cassaine	3	0.05–0.5	0.5–1	1	10	0.04	4/9 at 0.4[d,e]
A	2	...	...	10	3	2.9	1/3 at 8[e]
B	4	0.01–1	...	10	12	0.66	1/8 at 2
							0/2 at 8
C	2	0.05–1	10	...	4	1.3	0/1 at 8
D	4	0.5–5	10	10	11	0.69	3/7 at 2
							0/2 at 4
E	4	1–5	...	10	4	0.95	0/4 at 4
F	...	...	...	...	1	0.62	0/1 at 8
G	...	...	...	...	2	>4.0	
H	...	...	...	...	4	0.33	2/4 at 2 and 4[d,e]
I	6	0.1–0.5	5	5–10	6	0.23	4/5 at 2 and 4[d,e]
J	4	0.05–1	...	10	15	0.92	0/4 at 8
K	11	0.1–1	...	10	12	0.74	2/5 at 4[e]
L	12	0.5	...	5–10	4	0.76	1/4 at 2
							0/1 at 8[e]
M	2	5	10	1–10	6	0.94	1/3 at 8[e]
N	...	...	...	...	4	1.15	0/4 at 4
O	...	...	...	...	1	>1.0	
P	2	...	...	5–50	2	*f*	
Q	2	>10	>10	>10	2	3.5	0/1 at 8
R	4	0.01–1	...	10	4	>2.0	2/4 at 0.5 and 2.0[e]
S	2	0.5	...	5–10	4	0.57	1/3 at 4
T	4	1	...	5	3	0.78	2/3 at 1 and 8[e]
U	...	...	...	...	3	0.95	0/1 at 4
V	4	0.1–1	5	10	6	0.78	1/1 at 16[d]
W	2	0.5	...	10	2	>8.0	
X	4	0.1–1	...	5–10	2	*g*	
Y	...	...	...	...	2	1.4	0/1 at 6
Z	2	>10	>10	>10	3	*f*	0/3 at 4
AA	...	...	...	...	3	0.61	2/3 at 1 and 2[e]
BB	5	0.1–1	...	5	3	0.90	3/3 at 2 and 4[e]
CC	2	5	>10	>10	4	>2.0	2/4 at 2 and 4
							0/2 at 8
DD	5	1–5	>10	>10	3	1.9	0/3 at 4
EE	2	1	>10	>10	3	0.90	2/3 at 4[e]
15	3	0.5–1	...	5–10	2	3.0	0/1 at 4
18	2	...	...	10	2	1.4	0/1 at 4
19	2[h]	0.1–1[h]	10[h]	...	2	>1.00	
23c[i,j]	4	0.5–1	...	10	4	>8.0	0/2 at 8
23c[k]	2	0.05	...	0.5	4	4.0	0/3 at 8
24	2	>10	>10	>10	2	>2.0	

[a] A positive indication involves an increase in contractile force of greater than 10% over that present at the time of drug addition. [b] Concentrations and doses are expressed in terms of the base. [c] Respiratory arrest. [d] Ventricular fibrillation. [e] Asystole. [f] Depresses contractile force at doses up to 8 mg/kg. [g] Depresses contractile force at 2 mg/kg. [h] Run on isolated guinea pig atrium. [i] Isomer A. [j] A 5–10% increase was noted at 2 mg/kg. [k] Isomer B.

Respiratory arrest and ventricular fibrillation were observed in the animals anesthetized with both pentobarbital and α-chloralose; ventricular ectopic beats were observed only in the pentobarbitalized dogs (2/3 experiments). The lethal dose with cassaine in one dog experiment was 2.2 mg/kg.

Experimental Section[12]

General Procedure for Wittig Reaction. Ethyl *dl*-3,4,4aα,-4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-Δ$^{2(1H)}$.α-phenanthrenacetate (Mixture of Isomers 3 and 5).—A solution of sodium ethoxide [prepared from 1.6 g (0.070 g-atom) of sodium and absolute ethanol] in 120 ml of dry dimethylformamide (DMF) was cooled in an ice bath and treated dropwise with a solution of 15.5 g (0.070 mole) of triethyl phosphonoacetate in 20 ml of dry DMF with stirring. The resulting solution was stirred cold for 5 min and then a solution of 7.68 g (0.0346 mole) of *dl*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-dodecahydro-7β-hydroxy-2(1H)-phenanthrone[6] in 30 ml of dry DMF was added dropwise with stirring. This mixture was then stirred cold for 15 min and at room temperature for 2 hr. It was added to 1.5 l. of H_2O and the mixture was made acidic with 2 *N* HCl. The precipi-

(12) All melting points are corrected. Nmr spectra were determined on a Varian A-60 spectrophotometer using Me_4Si as an internal reference. The silica gel used for column chromatography (100–200 mesh) was obtained from the Davison Co., Baltimore, Md. The silica gel used for plate chromatography was grade P254, obtained from Brinkmann Instruments, Westbury, N. Y.

TABLE V
INTRAVENOUS INFUSION OF CARDIOTONIC COMPOUNDS INTO ANESTHETIZED DOGS

Compd	Rate of infusion, mg/kg/min	Time to contractile force ↑, min	Time to rate slowing, min	Time to give ventricular ectopic beats, min	Time to give convulsions, min	Lethality mg/kg	Lethality Time, min	Remarks
L, 2% sol + pentobarbital, 30 mg/kg iv	0.41	5.0	..	45	15	...	...	Tremors, A–V block, terminated at 170 min after 69.5 mg/kg
	1.11	1.3	..	30	..	41.1	37	Ventricular fibril, resp arrest at 33 min
	1.96	1.3	..	..	..	11.8	6	Resp arrest at 2 min
L, 2% sol + α-chloralose, 80 mg/kg iv	0.41	3.0	..	..	15	...	...	Severe tremors, terminated at 60 min after 24.5 mg/kg
	0.90	1.0	..	..	4	34.2	38	Clonic–tonic convulsions, resp arrest, ventricular fibril
	1.69	1.5	..	..	6	27.9	17	Tremors, clonic–tonic convulsions, ventricular fibril
Cassaine, 0.1% sol + pentobarbital, 30 mg/kg iv	0.0094	100	50	60	..	2.2	234	A–V block, ventricular ectopic tachycardia, cessation of resp, ventricular fibril

tated product was extracted with ether and the extracts were washed with brine and dried (Na_2SO_4). Removal of the ether gave an oily residue which partially crystallized upon addition of about 25 ml of ethanol. Dilution of this mixture with 300 ml of H_2O and filtration afforded 10.4 g (100%) of a crystalline product, mp 89–101°, which was shown by glpc to be a 1:1 mixture of *cis* and *trans* isomers together with 1.6% of an impurity. These isomers were not separable on silica chromatoplates developed with pure ether but this chromatographic process was used to remove the impurity. The isomer mixture was then recrystallized from ether–hexane to give compound B (Table I).

Ethyl *dl-trans*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (4).—A solution of 25.4 g (0.087 mole) of ethyl *dl*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-dodecahydro-7β-hydroxy-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (B, Table I) in 220 ml of pyridine was added in 2 min with stirring to a mixture of 21.9 g (0.22 mole) of CrO_3 and 220 ml of pyridine at room temperature and the resulting mixture was stirred overnight. Ethyl acetate (1.5 l.) was added, the mixture was filtered and the filtrate was concentrated to a residue by warming under reduced pressure. This residue was treated with 400 ml of ether and a further insoluble material was removed by filtration. Concentration of the ether solution and addition of hexane afforded 6.13 g of crystalline solid, mp 85–90°. Recrystallization from ether, with hexane added, gave 5.7 g of the *trans* isomer, mp 94–96°. Reworking all of the mother liquors furnished another 0.75 g of product, mp 94–97° (total yield 26%). The analytical sample, obtained from a similar experiment, is D (Table I).

***dl-cis*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetic Acid (9).**—The mother liquor residues from the preceding experiment were dissolved in 500 ml of 95% ethanol, 200 ml of 2 *N* aqueous NaOH was added, and the solution was refluxed in a nitrogen atmosphere for 1.25 hr. The reaction mixture was added to ice–water and neutralized with acetic acid, and the product was extracted with ether. The ether extracts were extracted with 2 *N* NaOH and these extracts were acidified with 2 *N* HCl. The precipitated carboxylic acid was collected and recrystallized from ethyl acetate to give 4.36 g of the *cis* acid, mp 206–214°, λ_{max}^{EtOH} 221 mμ (ε 15,700), and a second crop of 0.28 g, mp 202–213° (18%). The analytical sample of this acid (Table II, B) was obtained by hydrolysis of the pure *cis* methyl ester (**10**) using the general procedure for hydrolysis of alkyl esters.

Methyl *dl-cis*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (10).—The mother liquor residues from separation of the *cis* acid described immediately above contained 8.22 g (0.0313 mole) of the *cis* and *trans* unsaturated carboxylic acids. This solid, mp 180–195°, was dissolved in 250 ml of methanol, 0.10 mole of diazomethane in ether was added, and the solution was allowed to stand overnight. The solvent was removed and the crystalline residue was recrystallized from ether by the addition of hexane to give 2.87 g of material which melted at 100–130°. Two further recrystallizations furnished 1.6 g of the *cis* methyl ester **10** (Table I, E) which was shown by glpc to be a single compound.

General Procedure for Hydrolysis of Alkyl Esters. *dl-trans*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetic Acid (7).—A solution of 6.0 g (0.021 mole) of the ethyl ester (Table I, D) of the title compound in 200 ml of 95% ethanol was treated with 80 ml (0.16 mole) of 2 *N* aqueous NaOH and the solution was refluxed for 1.25 hr under N_2. The reaction mixture was cooled, acidified with acetic acid, and concentrated under reduced pressure until the ethanol was removed. The product was extracted from the resulting mixture with ether and then extracted from the ether with 2 *N* aqueous NaOH. Acidification of this extract with concentrated HCl precipitated the product which was collected and recrystallized from ethyl acetate to give 4.2 g of the *trans* acid C (Table II).

General Procedure for Making Basic Esters. 2-Dimethylaminoethyl *dl-trans*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (8).—A solution of 4.47 g (0.017 mole) of the *trans* acid **7** in 100 ml of THF was treated with 0.92 g (0.17 mole) of sodium methoxide and 1 ml of H_2O. The solvent was then removed by warming under reduced pressure, 20 ml of absolute ethanol was added and evaporated in the same manner and, finally, two 20-ml portions of dry benzene were added and evaporated. The resulting dry sodium salt was suspended in 150 ml of dry benzene, 3.46 g (0.044 mole) of pyridine was added, the mixture was immersed in an ice bath, and 40 ml of oxalyl chloride was added in a fast stream of drops with stirring. The mixture was removed from the ice bath, stirred for 10 min, and then concentrated as rapidly as possible under reduced pressure using a water bath at 45°. Application of heat was stopped as the last of the solvent evaporated and 150 ml of benzene was added followed by 40 ml of 2-dimethylaminoethanol in a rapid stream of drops with stirring and cooling. When addition was complete, the mixture was heated on the steam bath for 5 min, cooled, and diluted with 1 l. of ether and 600 ml of saturated aqueous Na_2CO_3. The layers were separated and the water layer was washed with ether and discarded.

The combined ether layers were extracted with two 100-ml portions and one 50-ml portion of 2 *N* HCl and the combined extracts were made basic with NaOH solution. This alkaline mixture was extracted with ether and the extracts were washed with brine and dried (Na_2SO_4). Removal of the ether afforded 4.9 g of a yellow oil which was (by glpc) a *trans–cis* (96:4) mixture of isomers together with 12% of impurity.

The product was purified by partition chromatography as described by Brown and Kupchan.[5] The solvent system employed was a 12:1:2:0.2 mixture of hexane–ethylene dichloride–methanol–H_2O. Supercel (300 g) was wetted with 225 ml of the polar phase containing 75 mg of brom cresol purple, the color

of the mixture was adjusted to a pale creamy yellow (faintly acid) by gaseous HCl, and the solid was packed into a column 9 cm in diameter. The sample was dispersed on 10 g of Supercel and placed on the top of the column. Elution of the column with the nonpolar phase of the solvent mixture developed the column; the position of all basic material was clearly revealed by blue bands. The product was recovered either by elution or slicing of the column, depending on the separation of the bands. In the present case the product was eluted to yield 4.39 g of the basic ester mixture which was free of significant impurities.

The 4.39 g of oil was dissolved in 200 ml of ether and treated with 1.11 ml of concentrated HCl in 20 ml of absolute alcohol. The precipitated hydrochloride salt was collected and recrystallized twice from acetone to give 3.56 g of *trans* basic ester, (Table III, B). A sample of the free base, regenerated from this salt, was shown by glpc to contain no *cis* isomer.

Isomerization during Conversion of a *trans* Unsaturated Acid to a Basic Ester.—A 2.95-g sample of *dl*-trans-3,4,4aα,4b,5,6,7,8,-8aα,9,10,10aβ-dodecahydro-4bβ-methyl-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetic acid (Table II, K) was converted to its 2-dimethylaminoethyl ester according to the general procedure except for the fact that the reaction time with oxalyl chloride was extended to 40 min and during removal of the excess oxalyl chloride, the reaction mixture was heated for about 10 min at 45° after the oxalyl chloride and benzene had evaporated. The basic ester was isolated in the standard manner and converted to its methanesulfonate salt without chromatography. The crude salt, mp 137–142°, weighed 3.5 g (74%) and two recrystallizations from ethyl acetate afforded 2.1 g of material melting at 144–147°. Glpc on the base regenerated from this salt showed a 1:1 mixture of *cis* and *trans* isomers and the melting point of this salt corresponded closely to that of 146–148° found for such an isomer mixture (Table III, J) prepared from a mixture of *cis* and *trans* acids.

***dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-4bβ-methyl-2(1H)-phenanthrone 7-*p*-Toluenesulfonate.**—A solution of 10.0 g (0.043 mole) of *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,-10aβ-dodecahydro-7β-hydroxy-4bβ-methyl-2(1H)-phenanthrone in 50 ml of pyridine was treated with 9.60 g (0.050 mole) of *p*-toluenesulfonyl chloride in 50 ml of pyridine and kept overnight at room temperature. The mixture was added to 150 ml of concentrated HCl and 350 ml of ice–water and this mixture was extracted with ether. The extract was washed with 2 *N* NaOH solution, dried ($MgSO_4$), and concentrated to a residue to give 16.4 g of the title compound as an amber oil: λ_{max}^{EtOH} 224, 256, 261, 267 and 273 mμ (ϵ 12,100, 660, 690, 590, and 470, respectively); λ_{max}^{film} 5.86, 6.28, 7.39, and 8.52 μ. This oil was used without further purification in the following experiment.

Detosylation of *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-4bβ-methyl-2(1H)-phenanthrone 7-*p*-Toluenesulfonate.—A solution of 16.3 g of the above oily tosylate in 100 ml of *s*-collidine was heated under reflux for 4 hr. The solution was cooled and poured into 400 ml of 2 *N* H_2SO_4. The acidic mixture was extracted with ether and the extract was washed with 2 *N* H_2SO_4, H_2O, and brine. It was dried ($MgSO_4$) and concentrated to a residue to give 7.0 g of an oil which was assumed to be a mixture of Δ^6- and Δ^7-2-phenanthrones. This mixture was hydrogenated in the following experiment without purification.

Hydrogenation of the Mixture of Δ^6- and Δ^7-2-Phenanthrones.—A solution of 0.69 g of the mixture of phenanthrones described in the preceding experiment in 25 ml of ethanol was treated with 0.10 g of 10% Pd–C and the mixture was shaken in a hydrogen atmosphere until 1 molar equiv was absorbed (5 min). The mixture was filtered and the filtrate was concentrated to a residue by warming under reduced pressure. The residue was dissolved in ether and the solution was dried ($MgSO_4$) and concentrated to give 0.56 g of crude ***dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,-10aβ-dodecahydro-4bβ-methyl-2(1H)-phenanthrone** as an amber oil. It was purified by column chromatography on 15 g of silica gel with elution by 1:9 ether–pentane. The resulting oily ketone showed a single spot by tlc, λ_{max}^{film} 5.83 μ, and an nmr peak ($CDCl_3$) at 0.75 ppm (*t*-CH_3) with no vinyl hydrogen peak. This oily ketone was used in the preparation of A, Table I.

Partial Separation of *cis* and *trans* Isomers of Ethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-4bβ-methyl-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (Table I, L and M).—Oxidation of the 3β-ol group of K (Table I) was accomplished on 26 g by the method used for making keto ester **4**. Recrystallization of the crude product once from acetone–hexane and twice from cyclohexane furnished 4.1 g (16%) of M, Table I, which is rich in the *cis* isomer. All of the mother liquor residues were combined and chromatographed on 300 g of silica gel. Ether–pentane (3:7) eluted the desired ester mixture without separation of the isomers. This crystalline material was recrystallized three times from cyclohexane to give 5.1 g (20%) of L, Table I, which was rich in the *trans* isomer.

Methyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-1β,4bβ-dimethyl-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (Table I, N).—To a suspension of 2.82 g (0.052 mole) of reagent sodium methoxide in 35 ml of dry 1,2-dimethoxyethane was added 9.5 g (0.052 mole) of trimethyl phosphonoacetate in 35 ml of dry 1,2-dimethoxyethane, and the mixture was stirred for 1 hr at room temperature. A solution of 6.5 g (0.026 mole) of 3,4,4aα,-4b,5,6,7,8,8aα,9,10,10aβ-dodecahydro-7β-hydroxy-1β,4bβ-dimethyl-2(1H)-phenanthrone[6] in 70 ml of 1,2-dimethoxyethane was added and the course of the reaction was followed by tlc. Silica plates developed with methanol–ether (1:49) showed that the reaction was about 50% complete in 1 hr but that it progressed no further even when the mixture was refluxed (84°) for 5 days. After the reflux period, 25 ml of H_2O and 500 ml of ether were added and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give 9.0 g of N, Table I, as a viscous oil which contained considerable unreacted ketone. This mixture was hydrolyzed directly, giving a carboxylic acid which was easily separable from ketonic impurity. The yield in this reaction was not increased when a 4:1 ratio of Wittig reagent to ketone was used.

In a similar experiment the product was purified by chromatography on silica gel, a process which did not separate the mixture of isomers. This product showed (by glpc) an isomer ratio of 3:7.

***dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-4bβ,8,8-trimethyl-2(1H)-phenanthrone.**—A solution of 3.4 g (0.013 mole) of 4,4aα,4b,5,6,7,8,8aα,9,10-decahydro-7β-hydroxy-4bβ,8,8-trimethyl-2(3H)-phenanthrone[2] in 30 ml each of THF and ether was added rapidly to 300 ml of liquid ammonia containing 0.364 g (0.052 g-atom) of Li. After addition was complete the reaction mixture was stirred for 1 min and solid NH_4Cl was then added to discharge the blue color. The ammonia was allowed to evaporate and ether and H_2O were added. The ether layer was separated, washed with brine, dried (Na_2SO_4), and concentrated. The residue was recrystallized from cyclohexane to give 0.90 g of product, mp 102–105°, and 0.91 g, mp 96–104°. The residue from the mother liquor was chromatographed on eight 20 × 40 cm silica gel coated chromatoplates which were developed with 1:1 ether–pentane. The product band was extracted and the product was recrystallized from cyclohexane to give 0.66 g of material, mp 103–108°, and 0.28 g, mp 100–102° (total, 2.75 g, 80%).

The combined material was used in this state of purity without characterization to form S of Table I.

***dl*-7,7-Ethylenedimercapto-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-dodecahydro-4bβ-methyl-$\Delta^{2(1H),\alpha}$-phenanthreneacetic Acid (Table II, G).**—A solution of 1.64 g (5.9 mmoles) of *dl*-3,4,4aα,-4b,5,6,7,8,8aα,9,10,10aβ-dodecahydro-4bβ-methyl-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetic acid (Table II, J) in 15 ml of acetic acid was treated with 2.0 ml of ethanedithiol followed by 2.0 ml of boron trifluoride etherate. No heat was evolved but a crystalline precipitate formed immediately. After 5 min the mixture was diluted with 15 ml of H_2O and filtered. The filter cake was washed well with water, air-dried, and recrystallized from 100 ml of acetic acid to give 1.56 g of G, Table II.

***dl*-7,7-(Ethylenedisulfonyl)-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-dodecahydro-$\Delta^{2(1H),\alpha}$-phenanthreneacetic Acid (Compound I, Table II).**—A solution of 1.2 g (3.5 mmoles) of *dl*-7,7-(ethylenedimercapto)-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-dodecahydro-$\Delta^{2(1H),\alpha}$-phenanthreneacetic acid (Table II, H), in 150 ml of ether was treated with 3.08 g (17 mmoles) of monoperphthalic acid in 21 ml of ether. After the solution stood overnight at room temperature, 150 ml of THF was added, and the solution was left for 3 more days. Ether (500 ml) was added and the solution was washed (saturated Na_2SO_3, NaCl) and then dried (Na_2SO_4). The solution was concentrated to give a crystalline residue which was triturated with about 20 ml of $CHCl_3$ and collected on a filter; 1.13 g, mp 266–267° dec. A second crop of 0.19 g, mp 267–270°, was obtained by concentration of the $CHCl_3$ washings (92% yield). Recrystallization from acetone gave compound I, Table II.

***dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-4bβ-methyl-7β-pyrrolidino-$\Delta^{2(1H),\alpha}$-phenanthreneacetic Acid (Table II, M).**

A mixture of 3.10 g (11.2 mmoles) of J, Table II, 75 ml of benzene, and 8 ml (96 mmoles) of pyrrolidine was heated under reflux for 4.5 hr with a water separator attached to the system. This solution was concentrated to a residue by warming under reduced pressure and the residue was treated with 50 ml of dry benzene and 3.5 ml (93 mmoles) of formic acid. The mixture was heated under reflux for 30 min, cooled, and treated with 1.5 ml of formic acid. Water (60 ml) and ether (100 ml) were added and the layers were separated. The ether layer was extracted once with 2 *N* HCl and discarded. Addition of the acidic extract to the aqueous portion of the reaction mixture caused precipitation of the hydrochloride salt of the product. Concentrated HCl (3 ml) and 10 ml of brine were added and the precipitate was collected. It was washed well with acetonitrile and then ether to give 2.57 g of crude M, Table II, which was suitable for conversion to a basic ester.

2-Dimethylaminoethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-dodecahydro-4bβ-methyl-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate Amidinohydrazone (Table III, H).—A solution of 5.60 g (0.0161 mole) of 2-dimethylaminoethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,-10aβ-dodecahydro-4bβ-methyl-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (Table III, D) and 1.2 ml of concentrated HCl in 25 ml of methanol was added to 175 ml of 1 *N* methanolic HCl in which had been dissolved 6.0 g (0.044 mole) of aminoguanidine bicarbonate. The solution was allowed to stand at room temperature for 41 hr and was then treated with solid $NaHCO_3$ until neutral. The solvents were removed by warming under reduced pressure and the residue was dissolved in 1:4 acetic acid–water. A small insoluble residue was removed by filtration and the filtrate was cooled in an ice bath while being made strongly alkaline with 35% aqueous NaOH. The precipitated product was collected and dried by addition and evaporation of several portions of ethyl acetate.

The 6.8-g residue was dissolved in 110 ml of methanol and the solution was treated with 2.8 ml of concentrated HCl and 500 ml of ether. This mixture stood for 64 hr and was then filtered to give 5.45 g of desired amidinohydrazone hydrochloride, mp 180–200° dec. It was recrystallized by dissolving it in methanol and adding ether to give perhaps a different polymorph because this material (4.07 g) melted at 167° dec (Table III, H).

2-Dimethylaminoethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-4bβ-methyl-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (Table III, K).—A 3.65-g sample (10.5 mmoles) of amorphous J, Table III, was dissolved in 100 ml of methanol and stirred while 0.53 g of $NaBH_4$ was added in small portions. The solution was allowed to stand overnight at room temperature, acidified with 2 *N* H_2SO_4, and concentrated by warming under reduced pressure until the methanol was removed. The aqueous residue was diluted with 250 ml of H_2O, washed with ether, and made alkaline with 2 *N* aqueous NaOH. The precipitated product was extracted with ether and the extracts were washed (H_2O, brine) and dried ($MgSO_4$). Concentration afforded 3.00 g of colorless, oily title compound which was converted to its hydrochloride salt (Table III, K).

Separation of *cis* and *trans* Isomers (Table III, L and M) of 2-Dimethylaminoethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-4bβ-methyl-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (Table III, K) by Fractional Crystallization of the Methanesulfonate Salts.—The amorphous base obtained from K of Table III (2.3 g, 6.6 mmoles) dissolved in 30 ml of ethyl acetate was treated with 0.53 g (5.5 mmoles and 17% less than theory through error) of methanesulfonic acid dissolved in 20 ml of ethyl acetate. The precipitate which formed was collected and recrystallized three times from acetonitrile to give 0.74 g (25%) of solid, mp 232–236° dec. One further recrystallization afforded the *trans* isomer (Table III, L).

Concentration of each of the three mother liquors separately in the above separation of the *trans* isomer of mp 232–236° afforded the more soluble *cis* isomer in crops of 0.20 g, mp 213–218°; 0.25 g, mp 218–221°; 0.20 g, mp 219–223°; total yield 0.65 g (22%). A single recrystallization from acetonitrile furnished the pure *cis* isomer (Table III, M).

2-Dimethylaminoethyl *dl-trans*-3,4,4aα,4b,5,6,7,8,8aα,9,10,-10aβ-Dodecahydro-7β-hydroxy-4bβ-methyl-$\Delta^{2(1H),\alpha}$-phenanthreneacetate 7-Acetate (Table III, N).—Compound L, Table III (2.00 g), was treated with 25 ml of H_2O and 3 ml of 2 *N* NaOH solution and the liberated base was separated with ether. The ether was evaporated and the residual oil was treated with 10 ml of pyridine and 5 ml of acetic anhydride for 16 hr. This mixture was diluted with 125 ml of H_2O and made strongly basic with 2 *N* NaOH. It was extracted twice with ether and the extracts were washed twice with brine, dried, and concentrated to give 1.78 g of a viscous, amber oil. The oily acetate was converted to 1.75 g of its hydrochloride salt, mp 175–180°. Two recrystallizations afforded N, Table III.

2-Dimethylaminoethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-4bβ-methyl-$\Delta^{2(1H),\alpha}$-phenanthreneacetate 7-Benzoate (Table III, O).—A solution of 0.90 g of the base from K, Table III, in 50 ml of dry benzene was treated with 0.5 ml of pyridine and 2.0 ml of benzoyl chloride and heated on the steam bath for 5 min. The solvents were removed by warming under reduced pressure and the residue was partitioned between 2 *N* aqueous NaOH and CH_2Cl_2. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to give 1.3 g of a crystalline residue. This base was dissolved in hot acetonitrile, 0.3 ml of 8 *N* alcoholic HCl was added, and the mixture was cooled to give the hydrochloride salt of the desired product. One recrystallization from acetonitrile furnished O of Table III.

2-Dimethylaminoethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-4bβ-methyl-$\Delta^{2(1H),\alpha}$-phenanthreneacetate 7-Nitrate (Table III, P).—Nitric acid (90%, 8 ml) was added slowly with stirring at −10 to 0° to 50 ml of acetic anhydride. Then a solution of 4.00 g (0.0115 mole) of the free base of K, Table III, in 15 ml of $CHCl_3$ was added dropwise with stirring at −5 to −10° in 15 min. This solution was kept cold for 1.5 hr and then poured into 400 ml of ice and water. The mixture was allowed to stand for 1 hr, made alkaline with concentrated NH_4OH, and extracted twice with ether. The extracts were washed with brine and concentrated to a residue by warming under reduced pressure.

The oily residue was chromatographed on silica gel coated plates which were developed with 1:1:98 methanol–isopropylamine–$CHCl_3$. The loading amounted to about 0.4 g/20 × 40 cm plate carrying a 1-mm coating of silica gel. The principal band from the plates afforded an oil whose infrared spectrum showed no hydroxyl absorption. The oil was desolvated under reduced pressure at 54°, dissolved in 10 ml of ether, and treated with 2.0 ml of 6 *N* alcoholic HCl. The precipitated solid was boiled with 15 ml of acetone and the mixture was cooled and filtered. The crystalline salt was then recrystallized by diluting a solution of it in 15 ml of warm methanol with ether to the point of cloudiness. Colorless blades separated. This mixture was diluted with 100 ml of ether and filtered to give P, Table III.

2-(Carbobenzoxyamino)ethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,-10aβ-Dodecahydro-4bβ-methyl-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (Table III, V).—A solution of 4.84 g (0.0175 mole) of J, Table II, in 30 ml of DMSO was treated with 0.99 g (0.018 mole) of sodium methoxide followed by 4.74 g (0.0183 mole) of benzyl 2-bromoethylcarbamate.[13] This mixture was allowed to stand for 1.25 hr at room temperature, heated at 100° for 4.25 hr, cooled, diluted with 150 ml of H_2O, and extracted twice with ether. Concentration of the extracts gave an oil (8 g) which was chromatographed on 22 20 × 40 cm silica chromatoplates developed with 1:4 ethyl acetate–$CHCl_3$. The oily product, thus purified, appeared by tlc to be better than 98% pure. It showed λ_{max}^{EtOH} 213, 217, and 223 mμ (ϵ 18,700, 18,600, and 17,000, respectively); λ_{max}^{film} 2.99 (ms) (NH), 5.85 (vs) and broad (C=O and ester), 6.09 (s) (*exo* C=C), and 6.55 μ (s) (NH deformation); nmr peaks ($CDCl_3$) at 7.28 (5 aromatic H), 5.5 (=CH—), 5.18 (N–H), 5.07 (benzyl CH_2), 3.42–4.13 (OCH_2), and 0.90 ppm ($\gtrless CCH_3$). The 6.13 g of oil (77%) was cleaved with trifluoroacetic acid as described below without further characterization.

2-Aminoethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-4bβ-methyl-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (Table III, W).—A solution of 3.59 g (0.0079 mole) of the carbobenzoxyamino ester described in the preceding experiment in 20 ml of commercial trifluoroacetic acid was allowed to stand for 24 hr. The solution was diluted with 30 ml of pentane, the mixture was stirred thoroughly, and the supernatant liquid was decanted from an oily layer. This process was repeated four times. Then 5 ml of ether was added, the mixture was stirred, 50 ml of pentane was added, and the supernatant liquid was decanted. This process was repeated twice. The oily product was then diluted with a few milliliters of acetone and streaked on ten 20 × 40 cm silica plates which were developed with 3:3:94 methanol–isopropylamine–$CHCl_3$. The principal bands were quickly scraped off and eluted with 1:19 isopropylamine–THF. The eluate

(13) E. Katchalski and D. B. Ishai, *J. Org. Chem.*, **15**, 1067 (1950).

was concentrated to a residue at 25° under reduced pressure, the flask was flushed free of isopropylamine with nitrogen and an additional 25 ml of THF was added and evaporated to remove traces of isopropylamine.

The residual oil was dissolved in 50 ml of THF and excess gaseous HCl was added. The amorphous precipitate was dissolved in 20 ml of 95% ethanol and this solution was diluted with 10 ml of acetone followed by 50 ml of ether which was added in increments to allow the precipitate to crystallize. The slightly sticky solid was triturated with 10 ml of acetone to give W of Table III.

N-(2-Dimethylaminoethyl) *dl*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetamide (Table III, Z).—The acid chloride of E, Table II, was prepared from 2.05 g (7.8 mmoles) of the acid in the standard manner used for preparation of basic esters. This acid chloride in 40 ml of dry benzene was treated with 10 g (114 mmoles) of N,N-dimethylethylenediamine and the mixture was heated on the steam bath for 5 min. Ether and saturated $NaHCO_3$ were added and the layers were separated. The ether layer was extracted with six 100-ml portions of 2 *N* HCl and the aqueous extracts were heated at 50° for 0.75 hr to cleave any enamine present from reaction at C-3. This aqueous solution was made basic with 35% NaOH, the product was extracted with ether, and the extracts were washed with brine, dried (Na_2SO_4), and concentrated. The resulting 1.8 g of oil was purified by partition chromatography (as described in the general procedure for making basic esters) using 60 g of Supercel. The principal band furnished 1.16 g of colorless oil. Conversion of this base to its methanesulfonate salt gave Z, Table III.

2-Dimethylaminoethyl *dl*-3,4,4aα,4bβ,5,6,7,8,8aβ,9,10,10aβ-Dodecahydro-7-oxo-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (Table III, CC).—This basic ester was prepared in the standard manner from 2.5 g of R of Table II. The 2.93 g of basic ester from the partition column was converted to its hydrochloride salt which was recrystallized three times to give 1.15 g of the title compound. The combined mother liquors from recrystallization were used in the next experiment.

2-Dimethylaminoethyl *dl*-3,4,4aα,4bβ,5,6,7,8,8aβ,9,10,10aβ-Dodecahydro-7α-hydroxy-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (Table III, DD).—The mother liquors from isolation and purification of CC, Table III, were treated with NaOH solution and the liberated base was isolated with ether. This base (1.27 g) was dissolved in 60 ml of 95% ethanol, 150 mg of $NaBH_4$ in 5 ml of H_2O was added, and the mixture was left standing for 1 hr at room temperature. Acetone and dilute HCl were added and the ethanol was removed by warming under reduced pressure. Ether was added, the layers were separated, and the ether layer was extracted with 2 *N* HCl. The combined layers were made alkaline with NaOH solution and extracted with ether. These extracts were washed with brine, dried (Na_2SO_4), and concentrated to give 1.2 g of crude title compound. This was subjected to partition chromatography as described in the general procedure for making basic esters. The resulting pure amino ester was converted to its hydrochloride salt, DD of Table III.

Ethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-4bβ-methyl-$\Delta^{2(1H),\alpha}$-phenanthrenepropionate (14).—A mixture of 24.3 g (0.102 mole) of triethyl phosphono-2-propionate, 11.4 g (0.102 mole) of potassium *t*-butoxide, and 200 ml of dry DMSO was stirred for 0.5 hr. To the resulting cloudy solution was added 8.00 g (0.034 mole) of *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-dodecahydro-7β-hydroxy-4bβ-methyl-2(1H)-phenanthrone[6] which dissolved immediately. This solution was heated at 58–60° for 22 hr, cooled, neutralized with 7 ml of acetic acid and diluted with 250 ml of saturated salt solution. The mixture was extracted four times with ether and the extracts were washed with brine and concentrated to a residue. Chromatography of the oily residue on 400 g of silica gel using 1:3 → 2:3 ether–pentane afforded 7.7 g (71%) of title compound. It showed a single spot on chromatoplates developed with 3:97 methanol–ether. Glpc indicated a 47:48 ratio of *cis–trans* isomers with about 5% impurity present. This product was hydrolyzed without further purification.

***dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-4bβ-methyl-$\Delta^{2(1H),\alpha}$-phenanthrenepropionate.**—This hydrolysis was run in the standard manner except that the solution was heated under reflux for 5.5 hr. Solid separated progressively as the ether extracts were concentrated to dryness. This acid (88%) had such poor crystallizing properties that it was used without further purification.

2-Dimethylaminoethyl *dl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-4bβ-methyl-$\Delta^{2(1H),\alpha}$-phenanthrenepropionate (15).—This basic ester was prepared from the corresponding acid, just described, in the standard manner except that the product was purified by plate chromatography instead of partition chromatography. Methanol–isopropylamine–$CHCl_3$ (2:2:96) was used to develop the plates. The resulting oily basic ester was converted to its hydrochloride salt which solidified when triturated with acetone. It was dissolved in a minimum of methanol and precipitated with ether to give a 1:1.3 *cis–trans* mixture of the desired product (40%). This salt is soluble in water to the extent of 0.5%.

Anal. Calcd for $C_{22}H_{41}NO_3 \cdot HCl$: C, 66.06; H, 9.58; Cl, 8.86; N, 3.50. Found: C, 65.8; H, 9.8; Cl, 8.5; N, 3.7.

Ethyl *dl*-3,4,4aα,9,10,10aβ-hexahydro-7-methoxy-$\Delta^{2(1H),\alpha}$-phenanthreneacetate was prepared by the reaction of 14.6 g (0.118 mole) of triethyl phosphonoacetate with 7.5 g (0.033 mole) of ketone **17**[6] using the general procedure for such Wittig reactions described earlier. The crude product was chromatographed on 350 g of silica gel. Elution with 1:9 ether–pentane afforded 8.8 g (90%) of the title compound, λ_{max}^{EtOH} 221, 279, and 288 mμ (ϵ 27,000, 2100, and 1950, respectively). The indicated a single compound. This product was used without further processing.

***dl*-3,4,4aα,9,10,10aβ-Hexahydro-7-methoxy-$\Delta^{2(1H),\alpha}$-phenanthreneacetic acid** was prepared from the ethyl ester described in the preceding experiment using the general procedure for hydrolysis of such esters described earlier. The crude product was recrystallized twice from acetone–hexane to give 1.58 g of product, mp 173–175.5°. Chromatography of the mother liquors afforded another 0.25 g of material melting at 173–175° (total yield, 23%). One additional recrystallization afforded the analytical sample: mp 174–175°; λ_{max}^{EtOH} 220, 279 and 288 mμ (ϵ 23,700, 2100, and 1900, respectively); nmr peaks ($CDCl_3$) at 7–7.8 (3 aromatic H), 6.4 (vinyl H), and 4.2 ppm (OCH_3).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 74.97; H, 7.40. Found: C, 75.1; H, 7.3.

2-Dimethylaminoethyl *dl*-3,4,4aα,9,10,10aβ-Hexahydro-7-methoxy-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (18) was prepared from the acid described in the preceding experiment using the general procedure for making such esters described earlier. Chromatography of the crude basic ester was not necessary. Recrystallization of the **hydrochloride salt** of the ester from acetone afforded an 81% yield of material melting at 173–181°. Further recrystallization from acetone afforded the analytical sample: mp 179–183°; λ_{max}^{EtOH} 222.5, 278, and 287 mμ (ϵ 26,500, 2200, and 2000, respectively); glpc showed a 1:1 mixture of *cis* and *trans* isomers.

Anal. Calcd for $C_{23}H_{39}NO_4 \cdot HCl$: C, 66.39; H, 7.96; N, 3.69. Found: C, 66.6; H, 8.1; N, 3.7.

2-Dimethylaminoethyl *dl*-3,4,4aα,9,10,10aβ-hexahydro-7-hydroxy-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (19) was prepared in the standard manner from T, Table II, with use of partition chromatography on 60 g of Supercel in the purification process. The **hydrochloride salt** crystallized when triturated with acetone (0.58 g, 38%) and melted at 204–219°. Recrystallization from acetone with ether added gave the analytical sample: mp 203–215°; λ_{max}^{EtOH} 224, 278, and 289 mμ (sh) (ϵ 25,700, 4650, and 3650, respectively); glpc showed a 1:1 mixture of *cis* and *trans* isomers.

Anal. Calcd for $C_{21}H_{37}NO_3 \cdot HCl$: C, 65.65; H, 7.71; Cl, 9.70. Found: C, 65.7; H, 7.8; Cl, 9.4.

Hydrogenation of Ethyl *dl*-3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Dodecahydro-7β-hydroxy-$\Delta^{2(1H),\alpha}$-phenanthreneacetate (Table I, B).—A solution of 12.0 g (0.041 mole) of the title compound in 300 ml absolute ethanol was hydrogenated at 3.9 kg/cm^2 and 25° for 2.5 hr in the presence of 1.2 g of 10% Pd–C. The mixture was filtered and the filtrate was concentrated to a residue by warming under reduced pressure. The residue was dissolved in ether and precipitated by addition of a small amount of hexane to give 4.43 g of material, mp 110–111.5°. Concentration of the filtrate gave 1.07 g of material, mp 106–108° (41%). Recrystallization from ether containing hexane afforded **ethyl *dl*-1,2,3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-tetradecahydro-7β-hydroxy-2ξ-phenanthreneacetate (isomer A) (23a)**, mp 110–111°.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.3; H, 10.2.

The mother liquor residues were greatly enriched in isomer B but the showed no separation of these isomers when using silica plates developed with 100% ether or 3:7 pentane–ether. These residues were hydrolyzed as described in the following experiment.

dl-**1,2,3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Tetradecahydro-7β-hydroxy-2ξ-phenanthreneacetic Acid (23b) (Isomer B).**—The mother liquor residues from the immediately preceding experiment were hydrolyzed according to the general procedure to give the title compound. Two recrystallizations from ethyl acetate and one from acetone afforded 3.13 g (29%, 2 steps) of **23b**, mp 164–166°. Further recrystallization from acetone afforded the analytical sample, mp 170–176°. Tlc analysis, done as with isomer A, indicated one compound was present, R_f 0.50.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.22; H, 9.83. Found: C, 72.3; H, 10.1.

dl-**1,2,3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Tetradecahydro-7β-hydroxy-2ξ-phenanthreneacetic Acid (23b) (Isomer A).**—The ester **23a** (4.5 g) was hydrolyzed according to the general procedure and the product was recrystallized once from ethyl acetate to give 3.95 g (97%) of the title compound, mp 214–216°. Tlc analysis on a silica gel plate using acetic acid–$CHCl_3$ (3:97) for development indicated that one compound was present, R_f 0.56. Further recrystallization gave mp 214.5–215.5°.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.22; H, 9.83. Found: C, 72.5; H, 9.8.

Dimethylaminoethyl *dl*-1,2,3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-Tetradecahydro-7β-hydroxy-2ξ-phenanthreneacetate (23c, Isomer A).—This basic ester was prepared from 3.5 g of **23b**, isomer A, in the standard manner to give 4.3 g of basic oil which was purified by partition chromatography on 300 g of Supercel as described in the general procedure. The major band was eluted and the recovered oil was converted to 3.2 g (64%) of the **hydrochloride salt** of the title compound, mp 247–251°. Recrystallization from methanol with ether added afforded the analytical sample, mp 255–257°. The free base, liberated from this salt, could not be distinguished from isomer B base by glpc.

Anal. Calcd for $C_{29}H_{35}NO_3 \cdot HCl$: C, 64.24; H, 9.71; Cl, 9.48. Found: C, 64.1; H, 9.9; Cl, 9.5.

Dimethylaminoethyl *dl*-1,2,3,4,4aα,4bβ,5,6,7,8,8aα,9,10,10aβ-tetradecahydro-7β-hydroxy-2ξ-phenanthreneacetate (23c) (isomer B) was prepared from 2.2 g of **23b**, isomer B, in the standard manner to give 2.53 g (81%) of the title compound as its **hydrochloride salt**, mp 196–206°. One recrystallization from acetone raised this melting point to 202–213° and it was unchanged upon further recrystallization.

Anal. Calcd for $C_{29}H_{35}NO_3 \cdot HCl$: C, 64.24; H, 9.71; Cl, 9.48. Found: C, 64.4; H, 9.8; Cl, 9.4.

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Cassaine Analogs. IV. Distant Analogs of Cassaine

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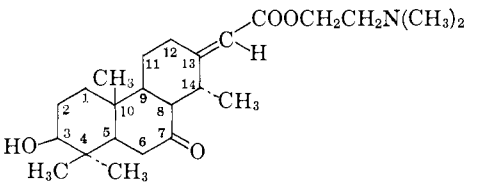
Basic esters have been made which bear a distant resemblance to the *Erythrophleum* alkaloid cassaine. These monocyclic and bicyclic analogs were needed in order to define the role of the skeleton and various substituents of cassaine in its cardiac action.

The *Erythrophleum* alkaloid cassaine (**1**) is reported to be quite similar to digitalis in its action as a cardiac stimulant.[1] Both of these drugs suffer from the dis-



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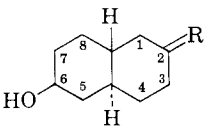
advantage of producing toxic symptoms in doses only slightly higher than those producing therapeutic effects. It was of particular interest to determine the role of the skeletal structure and the various substituents of cassaine in the cardiotonic activity and toxicity demonstrated by this alkaloid. In papers II[2] and III[3] of this series we have described a large number of basic esters which bear a rather close resemblance to cassaine. Presently we report some more distant analogs of this compound.

The bicyclic analog **5** was prepared from the *trans* ketone **2**. A Wittig reaction using trimethyl phosphonoacetate transformed **2** into the α,β-unsaturated ester **3** which was a roughly 1:1 mixture of *cis* and *trans* isomers (about the double bond). No effort was made in the presently reported work to separate these isomers since it was found in the series of closer analogs[2] that there were only slight differences in the cardiotonic activity of such *cis* and *trans* isomers.



2, R = O
3, R = CHCOOCH$_3$
4, R = CHCOOH
5, R = CHCOOCH$_2$CH$_2$N(CH$_3$)$_2$

Hydrolysis of ester **3** was accomplished with NaOH in aqueous ethanol to give carboxylic acid **4**. Basic ester **5** was then formed by the reaction of 2-dimethylaminoethanol on the acid chloride of **4**. This acid chloride was best prepared by treating the sodium salt of **4** with excess oxalyl chloride in the presence of pyridine. Any intermediate function formed at C-6 from attack there by oxalyl chloride was decomposed by the treatment with 2-dimethylaminoethanol; the 6-hydroxy basic ester was isolated.[2] Incidentally, the 6-acetate ester of **5** was also prepared.

This same sequence of reactions was used in the preparation of all of the basic esters reported here.

(1) See F. Erjavec and Š. Adamič, *Arch. Intern. Pharmacodyn.*, **155**, 251 (1965); E. L. McCawley, *Alkaloids*, **5**, 101 (1955), and references therein.

(2) R. L. Clarke, S. J. Daum, P. E. Shaw, T. G. Brown, Jr., G. E. Groblewski, and W. V. O'Connor, *J. Med. Chem.*, **10**, 582 (1967).

(3) S. J. Daum, M. M. Riano, P. E. Shaw, and R. L. Clarke, *J. Org. Chem.* **32**, 1435 (1967).