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 $C_{20}H_{35}NO_3 \cdot HCl$: 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,9,10,10$\alpha\beta$-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 $C_{20}H_{35}NO_3 \cdot HCl$: C, 64.24; H, 9.71; Cl, 9.48. Found: C, 64.4; H, 9.8; Cl, 9.4.

Acknowledgments.—Appreciation is expressed to Mrs. G. A. Snyder and Mrs. J. T. Dunn for technical assistance and to the Physical and Analytical Sections of the Sterling-Winthrop Research Institute for spectral and analytical determinations.

Cassaine Analogs. IV. Distant Analogs of Cassaine

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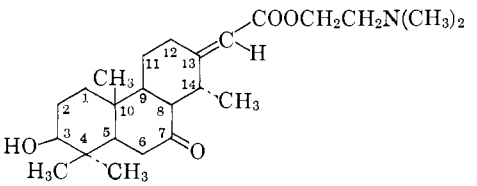
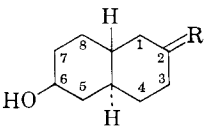
Basic esters have been made which bear a distant resemblance to the *Erythrophleum* alkaloid cassaine. These monocyclic and bicyclic analogs were needed in order to define the role of the skeleton and various substituents of cassaine in its cardiac action.

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 disadvantage 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.



1

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$_3$)$_2$

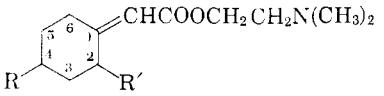
Hydrolysis of ester **3** was accomplished with NaOH in aqueous ethanol to give carboxylic acid **4**. Basic ester **5** was then formed by the reaction of 2-dimethylaminoethanol on the acid chloride of **4**. This acid chloride was best prepared by treating the sodium salt of **4** with excess oxalyl 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.

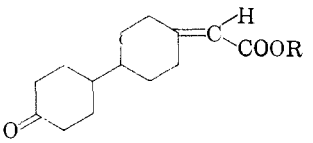
(1) See F. Erjavec and Š. Adamič, *Arch. Intern. Pharmacodyn.*, **155**, 251 (1965); E. L. McCawley, *Alkaloids*, **5**, 101 (1955), and references therein.
(2) R. L. Clarke, S. J. Daum, P. E. Shaw, T. G. Brown, Jr., G. E. Groblewski, and W. V. O'Connor, *J. Med. Chem.*, **10**, 582 (1967).
(3) S. J. Daum, M. M. Riano, P. E. Shaw, and R. L. Clarke, *J. Org. Chem.* **32**, 1435 (1967).

Therefore, these model reactions are described in the Experimental Section as general procedures and only specific deviations, physical properties, and analyses are reported under titles of individual compounds.

An even simpler group of ester analogs is represented by structures **6**–**8**. The required acid chloride intermediates for **6** and **7** were prepared by the action of



6, R = H; R′ = H
7, R = H; R′ = CH_3
8, R = OH; R′ = H

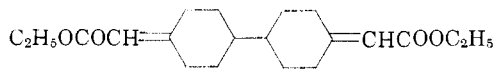


9, R = $CH_2CH_2N(CH_3)_2$
10, R = C_2H_5

$SOCl_2$ on the required carboxylic acid since no hydroxyl group was present at C-4.

A serious inconvenience in all the work reported here and earlier[2,3] has been the necessity for working with *cis–trans* mixtures of unsaturated esters and acids having broad melting ranges and poor crystallizing properties. Ester **9**, representing only rings A and C of cassaine, has an axis of rotational symmetry which permits no *cis–trans* isomerism. It is also attractive from the standpoint of having the required[2] C-3 and C-13 (cassaine numbering) functional groups held with the proper separation. These considerations prompted the synthesis of several compounds of this type.

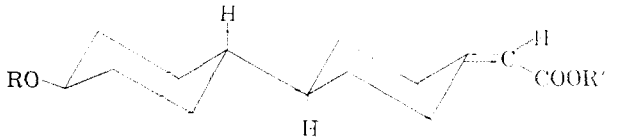
Bicyclohexyl-4,4′-dione, readily available from *p,p′*-bisphenol by the method of Wilds, Shunk, and Hoffman,[4] was treated with 1 molar equiv (+7%) of triethyl phosphonoacetate to give the required ester **10** (35%) together with 37% of starting material and 6% of diethyl bicyclohexyl-$\Delta^{1,\alpha;1',\alpha'}$-diacetate (**11**). Ester **10** was then converted to basic ester **9** in the standard manner.



11

Basic ester **9** turned out to be an oil which failed to form a crystalline hydrochloride, nitrate, sulfate, phosphate, or 1,5-naphthalenedisulfonate salt. A solution of the basic ester in 2 *N* HCl or an aqueous solution of ester hydrochloride began a slow precipitation of the corresponding carboxylic acid within a few minutes. Such instability to hydrolysis was not noted in any of the other basic esters reported here or earlier.[2] The A-ring ketone of this flexible molecule must somehow be involved since the corresponding hydroxy ester **14** is stable. Basic esters in the rigid tricyclic series[2] bearing a keto group in ring A are also stable to these mild conditions.

Reduction of keto ester **10** with lithium aluminum tri-*t*-butoxyhydride produced hydroxy ester **12**. This sharply melting product is a *dl* mixture of a single geometric isomer. The equatorial character of the hydroxyl group is assumed on the basis of the known course of reduction of unhindered ketones by this reagent.[5]



12, R = H; R′ = C_2H_5
13, R = H; R′ = H
14, R = H; R′ = $CH_2CH_2N(CH_3)_2$
15, R = *t*-C_4H_9; R′ = C_2H_5
16, R = *t*-C_4H_9; R′ = H
17, R = *t*-C_4H_9; R′ = $CH_2CH_2N(CH_3)_2$
18, R = C_6H_5NHCO; R′ = C_2H_5
19, R = C_6H_5NHCO; R′ = H
20, R = C_6H_5NHCO; R′ = $CH_2CH_2N(CH_3)_2$

Hydrolysis of **12** gave acid **13** which was converted to basic ester **14**. The hydrochloride and phosphate salts of this ester were quite stable in aqueous solution in contrast to the instability of the above-mentioned ketone analog. Acid **13** was readily resolved by fractional crystallization of its 1-(1-naphthyl)ethylamine salts but these optically active acids were not converted to optically active basic esters when it was found that *dl*-ester **14** had only slight cardiotonic activity.

Two hydroxyl group derivatives of ester **14**, the *t*-butyl ether **17** and the phenylurethan **20**, were prepared. The required hydroxyl derivatives were made at the ethyl ester stage (**15** and **18**) and converted to basic esters in the standard manner *via* acids **16** and **19**.

The cardiotonic activity of these more distant analogs of cassaine is reported in Table I along with the corresponding data for cassaine. For a comparison with some closer analogs and for details of the testing procedures, see the accompanying paper.[2]

TABLE I
CARDIOTONIC ACTION AND TOXICITY OF CASSAINE ANALOGS IN THE INTACT ANESTHETIZED[a] DOG VENTRICLE

Compd	No. of expts	Dose producing a 20% contractile force, mg/kg[b] iv	Mortality at higher doses, mg/kg
Cassaine	10	0.04	4/9 at 0.4
5	1	1.3	0/2 at 4
5-acetate	2	3.6	1/1 at 8
6	Decrease in force observed		
7	Decrease in force observed		
8	2	>8.0	1/2 at 32
9	4	1.3	3/4 at 2 and 4[c]
14·HCl	3	1.6	0/3 at 4
14·H_3PO_4	4	>4.0	1/4 at 2[d]

[a] Anesthetized with pentobarbital at 30 mg/kg. [b] Dose calculated as the free base. [c] Respiratory arrest. [d] Asystole.

Experimental Section[6]

General Procedure for Wittig Reactions. Methyl *dl*-3,4,4aα,5,6,7,8,8aβ-Octahydro-6β-hydroxy-$\Delta^{2(OH),\alpha}$-naphthaleneacetate (3).—A solution of 8.41 g (0.156 mole) of sodium methoxide and 28.1 g (0.154 mole) of trimethyl phosphonoacetate in 125 ml of dry dimethylformamide (DMF) was stirred for 5 min at room

(4) A. L. Wilds, C. H. Shunk, and C. H. Hoffman, *J. Am. Chem. Soc.*, **76**, 1753 (1954).

(5) O. H. Wheeler and J. L. Mateos, *Chem. Ind.* (London), 395 (1957).

(6) All melting points are corrected. The infrared spectra were recorded on a Perkin-Elmer infrared spectrophotometer, Model 21. The ultraviolet spectra were recorded on a Cary spectrophotometer, Model 15. The silica gel (100–200 mesh) used for column chromatography was obtained from the Davison Co., Baltimore, Md. That used for plate chromatography was type P 254, Brinckmann Instruments, Westbury, N. Y.

temperature and then a solution of 13.15 g (0.0783 mole) of *dl*-3,4,4aα,5,6,7,8,8aβ-octahydro-6β-hydroxy-2(1H)-naphthalenone (**2**)[7] in 33 ml of dry DMF was added in a single portion. This mixture was stirred at room temperature for 45 min, poured into ice and water and neutralized with 2 *N* HCl. The product was extracted with ether, and the extracts were washed with brine and concentrated to effect precipitation of 4.4 g of Wittig product, mp 74–90°. The mother liquor residue was chromatographed on 250 g of silica gel using 1:4 → 1:1 ether–pentane to elute an additional 3.76 g of product, mp 74–77°. A 14% recovery of starting material was also obtained from the column. The 8.16 g (47%) of product was recrystallized from ether with hexane added to give 3.45 g of **3**, mp 79–97°, λ_{max}^{EtOH} 221 mμ (ϵ 17,000), 1:2 *cis–trans* isomer mixture (by glpc).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.98. Found: C, 69.5; H, 8.8.

General Procedure for Preparation of Unsaturated Acids. *dl*-3,4,4aα,5,6,7,8,8aβ-Octahydro-6β-hydroxy-$\Delta^{2(1H),\alpha}$-naphthaleneacetic Acid (4).—A solution of 5.5 g (0.025 mole) of methyl *dl*-3,4,4aα,5,6,7,8,8aβ-octahydro-6β-hydroxy-$\Delta^{2(1H),\alpha}$-naphthaleneacetate (**3**) in 170 ml of 95% ethanol was treated with 68 ml (0.14 mole) of 2 *N* aqueous NaOH and heated under reflux for 1.5 hr. The alcohol was removed by warming under reduced pressure and the aqueous solution (with more H_2O added if the sodium salt of the product had partially precipitated) was washed with ether. The aqueous solution was acidified with 2 *N* HCl and the precipitated acid was collected on a filter if it crystallized. In the present case the precipitate was oily and was separated by ether extraction. The extract was washed with brine, dried (Na_2SO_4), and concentrated to a residue which crystallized upon trituration with ethyl acetate. Two recrystallizations from ethyl acetate gave 3.0 g (58%) of acid **4**, mp 170–189°, λ_{max}^{EtOH} 221 mμ (ϵ 15,900).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.56; H, 8.63. Found: C, 68.7; H, 8.6.

General Procedure for Making Basic Esters. 2-Dimethylaminoethyl *dl*-3,4,4aα,5,6,7,8,8aβ-Octahydro-6β-hydroxy-$\Delta^{2(1H),\alpha}$-naphthaleneacetate (5).—A solution of 7.95 g (0.0378 mole) of *dl*-3,4,4aα,5,6,7,8,8aβ-octahydro-6β-hydroxy-$\Delta^{2(1H),\alpha}$-naphthaleneacetic acid (**4**) in 150 ml of THF was treated with 2.04 g (0.0378 mole) of sodium methoxide, and the mixture was stirred for 5 min and concentrated to a residue by warming under reduced pressure. A suspension of the residue in 150 ml of dry benzene and 7 ml of pyridine was stirred in an ice bath while 50 ml of oxayl chloride was added. This mixture was stirred for 5 min cold and for 30 min at room temperature and then concentrated to a residue at <40°. A suspension of the residue in 50 ml of benzene was treated with 50 ml of 2-dimethylaminoethanol with cooling and stirring, and this mixture was heated on the steam bath for 10 min. It was cooled and diluted with 800 ml of ether and 600 ml of saturated Na_2CO_3 solution. 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 of 2 *N* HCl, and the combined extracts were made basic with NaOH solution. The alkaline mixture was extracted with ether and the extracts were washed with brine and dried (Na_2SO_4). Removal of the ether afforded the crude basic ester.

The crude basic ester was purified by partition chromatography as described by Brown and Kupchan.[8] The solvent system employed was a 12:1:2:0.2 mixture of hexane–ethylene dichloride–methanol–H_2O. Supercel (360 g) was wetted with 275 ml of the polar phase containing 90 mg of bromocresol 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 16 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 7.74 g (73%) of **5** as an oil.

The **hydrochloride salt** was prepared from this oil and recrystallized from acetone to give 5.7 g of material, mp 173–185°, λ_{max}^{EtOH} 226 mμ (ϵ 17,600). A sample of this salt was converted to the free base which was found by glpc to be a 1.2:1 *trans–cis* isomer mixture. For configurational assignment see ref. 3.

Anal. Calcd for $C_{16}H_{27}NO_3 \cdot HCl$: C, 60.46; H, 8.88; Cl, 11.15. Found: C, 60.4; H, 8.6; Cl, 11.4.

The **3-acetate ester hydrochloride** of **5** was prepared by treating 2.12 g of **5** with 10 ml of acetic anhydride and 10 ml of pyridine overnight at room temperature. The solution was diluted with cold water, made strongly basic with dilute NaOH, and extracted with ether. The extract was washed with brine and concentrated to a residue which was purified by partition chromatography as described above but using 60 g of Supercel. The less polar of the two bands contained 1.79 g (73%) of the desired acetate. It was converted to its hydrochloride salt which was recrystallized by dissolution in acetone followed by addition of ethyl acetate with boiling until the acetone was largely removed. This salt melted at 160–195° and was a 1:1.4 *trans–cis* isomer mixture (glpc on base).

Anal. Calcd for $C_{18}H_{29}NO_4 \cdot HCl$: C, 60.07; H, 8.40; Cl, 9.85. Found: C, 60.0; H, 8.1; Cl, 9.7.

2-Dimethylaminoethyl $\Delta^{1,\alpha}$-Cyclohexaneacetate (6).—A solution of 31.0 g (0.221 mole) of $\Delta^{1,\alpha}$-cyclohexaneacetic acid[9] in 300 ml of dry benzene was treated with 60 ml of $SOCl_2$ and heated under reflux for 2 hr. The solvents were removed by warming under reduced pressure and the residue was dissolved in 300 ml of dry benzene. 2-Dimethylaminoethanol (60 ml) was added dropwise with stirring and cooling, and the resulting mixture was then heated under reflux for 2 hr. The mixture was cooled, diluted with 2 l. of ether, and extracted twice with 2 *N* HCl, the second extract's being strongly acidic. The combined extracts were made alkaline with 35% NaOH with cooling, and the liberated base was extracted with ether. These ether extracts were washed with water and brine, dried ($MgSO_4$), and concentrated to give 37.3 g of brown, oily basic ester **6**.

A solution of this oil in 500 ml of ether was treated with 20.4 ml of 8.7 *N* ethanolic HCl and the precipitate was collected and recrystallized from acetone to give 35.0 g (64%) of the **hydrochloride salt** of **6**, mp 172–174°. One further recrystallization from acetone gave the analytical sample, mp 173–174°, λ_{max}^{EtOH} 224 mμ (ϵ 16,900).

Anal. Calcd for $C_{12}H_{21}NO_2 \cdot HCl$: C, 58.17; H, 8.95; Cl, 14.31. Found: C, 58.4; H, 8.8; Cl, 14.5.

2-Dimethylaminoethyl 2-methyl-$\Delta^{1,\alpha}$-cyclohexaneacetate (7) was prepared from an oily, unseparated mixture of *cis* and *trans* forms of 2-methyl-$\Delta^{1,\alpha}$-cyclohexaneacetic acid[10] by means of the procedure described in the preceding experiment. The crude base was converted to its **hydrochloride salt** which was recrystallized three times from acetone to give crystals, mp 129–131° (13%).

Anal. Calcd for $C_{13}H_{23}NO_2 \cdot HCl$: C, 59.65; H, 9.24; Cl, 13.55. Found: C, 59.5; H, 9.1; Cl, 13.4.

Ethyl 4-hydroxy-$\Delta^{1,\alpha}$-cyclohexaneacetate was prepared from 24.2 g of 4-hydroxycyclohexanone[11] using the general Wittig procedure described above. Tlc on a silica chromatoplate developed with 1:49 methanol–ether showed that the reaction was complete in about 5 min. The crude product was distilled and the portion which boiled at 114–142° (0.1 mm) was collected. This oil (34.5 g) was chromatographed on 500 g of silica gel using 1:1 ether–pentane for elution. The principal product from the column was then distilled to give 26.0 g (67%) of pure title compound, bp 119–121° (0.3 mm), which showed a single spot by tlc.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.20; H, 8.75. Found: C, 65.3; H, 9.0.

4-Hydroxy-$\Delta^{1,\alpha}$-cyclohexaneacetic acid was prepared by hydrolysis of 21.6 g of ethyl 4-hydroxy-$\Delta^{1,\alpha}$-cyclohexaneacetate in the standard manner. When the aqueous solution containing

(7) R. L. Clarke and C. M. Martini, *J. Am. Chem. Soc.*, **81**, 5716 (1959).

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

(9) This compound has been reported by V. J. Harding, W. N. Haworth, and W. H. Perkin, Jr., *J. Chem. Soc.*, **93**, 1943 (1908), but is most readily prepared from cyclohexanone by the Wittig reaction followed by hydrolysis according to our general procedures.

(10) H. Hauth, D. Stauffacher, P. Niklaus, and A. Malera, *Helv. Chim. Acta*, **48**, 1087 (1965), obtained a mixture of *cis* and *trans* ethyl 2-methyl-$\Delta^{1,\alpha}$-cyclohexaneacetate from the reaction of triethyl phosphonoacetate with 2-methylcyclohexanone. Preparative glpc was used to separate the isomers which were then hydrolyzed to the corresponding acids. No experimental detail was given. We used our standard procedures on 2-methylcyclohexanone without separation of isomers to give an oily mixture of ethyl esters and an oily mixture of acids.

(11) J. B. Aldersley, G. N. Burkhardt, A. E. Gillam, and N. C. Hindley, *J. Chem. Soc.*, 10 (1940).

the sodium salt of the product was acidified, 6.50 g (35%) of crystalline acid precipitated, mp 145–149°. One recrystallization of this product from ethyl acetate afforded 6.05 g of crystals of the desired acid, mp 150–152° and unchanged upon further recrystallization. The solution from which the solid separated was saturated with salt and extracted with ether. Concentration of the extracts gave an oil which crystallized poorly and was a mixture of two substances with only slightly different R_f values. The mixture was not investigated.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.51; H, 7.74. Found: C, 61.5; H, 7.9.

2-Dimethylaminoethyl 4-hydroxycyclohexyl-$\Delta^{1,\alpha}$-cyclohexaneacetate (8) was prepared in the standard manner from 16.5 g of 4-hydroxycyclohexyl-$\Delta^{1,\alpha}$-cyclohexaneacetic acid using oxalyl chloride. The crude basic ester was purified in two portions by partition chromatography using 360 g of Supercel for each portion. The purified base was converted to its **hydrochloride salt** which was recrystallized from acetonitrile to give 12.5 g (45%) of the desired salt, mp 159–162°. Two further recrystallizations gave the analytical sample, mp 163.5–166°.

Anal. Calcd for $C_{12}H_{23}NO_3 \cdot HCl$: C, 54.65; H, 8.41; Cl, 13.45. Found: C, 54.4; H, 8.4; Cl, 13.5.

Ethyl 4-(4-Oxocyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetate (10).—To a solution of sodium ethoxide, prepared from 8.6 g (0.37 g-atom) of sodium, in 850 ml of dry DMF at 10–20°, was added with stirring 83.3 g (0.37 mole) of triethyl phosphonoacetate in 20 min and stirring was continued for 30 min more. This solution was then added dropwise with vigorous stirring to a solution of 67.1 g (0.340 mole) of bicyclohexyl-4,4'-dione[4] in 325 ml of dry DMF at 15–20° in 1.5 hr. The resulting solution was allowed to stand at room temperature for 2 hr and was then poured into 5 l. of saturated salt solution. This mixture was extracted three times with ether and the extracts were dried (Na_2SO_4) and concentrated to give 107.5 g of an oily residue. This was chromatographed on 1.5 kg of silica gel. Elution with ether–pentane (1:9) removed 8 g of **diethyl bicyclohexyl-$\Delta^{4,\alpha;4',\alpha'}$-diacetate (11).** The melting point of this presumably *cis–trans* mixture was 60–69° after one recrystallization from methanol and 62–71° after a second recrystallization [7.05 g, 6% λ_{max}^{EtOH} 224 mμ (ε 36,000)].

Anal. Calcd for $C_{20}H_{34}O_4$: C, 71.83; H, 9.04. Found: C, 71.8; H, 8.8.

Elution of the chromatographic column with ether–pentane (1:4) removed 34.6 g of **10** which, after a single recrystallization from hexane, afforded 32.4 g (35%) of material melting at 56–58°, λ_{max}^{EtOH} 221 mμ (ε 17,400), λ_{max}^{KBr} 5.85 and 5.90 (carbonyls) and 6.14 μ (*exo* double bond).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.70; H, 9.15. Found: C, 72.5; H, 9.2.

Elution of the column with pure ether removed 24.6 g (37%) of unchanged starting material.

4-(4-Oxocyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid.—A solution of 51.4 g (0.195 mole) of ethyl 4-(4-oxocyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetate in 850 ml of absolute ethanol was treated with 145 ml of 2 *N* aqueous NaOH and allowed to stand overnight. Work-up in the standard manner afforded 36 g of acid which was recrystallized twice from acetonitrile to give 25.9 g (56%) of product, mp 161.5–164.5° and unchanged upon further recrystallization, λ_{max}^{EtOH} 220 mμ (ε 15,500).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; neut equiv, 236. Found: C, 71.3; H, 8.6; neut equiv, 240.

2-Dimethylaminoethyl 4-(4-Oxocyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetate (9).—The title compound was prepared in the standard manner from 17.4 g (0.074 mole) of 4-(4-oxocyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetic acid. At the point where the product was normally purified by partition chromatography, the present product (14.6 g) was chromatographed on 600 g of silica gel using a 0.5:0.5:70:29 mixture of methanol–isopropylamine–ether–pentane for elution. This afforded 6.91 g of oil which still was slightly impure (by tlc). A portion of this oil was used in unsuccessful attempts to obtain crystalline nitrate, hydrochloride, and 1,5-naphthalenedisulfonate salts.

The remaining 5.8 g of oily product was dissolved in 25 ml of 2 *N* HCl. The resulting clear solution became cloudy within 2 min. It was allowed to stand for 30 min, washed twice with ether, and filtered through Supercel. It was made alkaline with concentrated NH_4OH and the precipitated oil was extracted with two portions of ether. The extracts were dried (Na_2SO_4) and concentrated to give 4.1 g of a pale green oil.

The green oil was subjected to partition chromatography on 300 g of Supercel using the method described in the general procedure for making basic esters. Concentration of the eluate under reduced pressure with a final drying period of 2 hr at 50° and 0.2 mm pressure afforded 2.72 g (12%) of the desired basic ester (**9**) as a pale green oil, $\lambda_{max}^{95\%}$ 223.5 mμ (ε 17,600). The nmr spectrum was consistent with the assigned structure. This base failed to form a crystalline hydrochloride, sulfate, or phosphate salt.

Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.33; H, 9.51; N, 4.56. Found: C, 70.5; H, 9.3; N, 4.8.

Ethyl *dl*-4-(4-Hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetate (12).—A solution of 2.00 g (0.0076 mole) of **10** in 25 ml of dry THF was added dropwise with stirring to a solution of 3.00 g (0.012 mole) of lithium aluminum tri-*t*-butoxyhydride in 35 ml of dry THF at 5–10°. The resulting solution was stirred for 30 min, treated with 2 ml of acetic acid, and concentrated to a residue by warming under reduced pressure. The residue was dissolved in H_2O and ether, the layers were separated, and the ether layer was washed with dilute HCl. Concentration of this ether solution afforded 1.93 g of crystalline solid. Recrystallization of the solid twice from acetonitrile afforded 1.00 g (50%) of the desired hydroxy ester **12**, mp 102–103°, which was shown by vapor phase chromatography to be 99.1% pure.

Anal. Calcd for $C_{16}H_{28}O_3$: C, 72.16; H, 9.84; Found: C, 71.9; H, 9.7.

***dl*-4-(4-Hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid (13).**—Compound **12** was hydrolyzed in the standard manner except that the reaction mixture was allowed to stand overnight instead of being heated under reflux. Recrystallization of the acidic product from ethyl acetate afforded a 44% yield of material which melted at 182–186° in an open capillary tube and at 185–187.5° in an evacuated tube.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 70.60; H, 9.31; neut equiv, 238.3. Found: C, 70.9; H, 9.6; neut equiv, 240.

The ether extract of the alkaline reaction mixture furnished 30% of recovered starting material.

***l*-4-(4-Hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid *l*-1-(1-Naphthyl)ethylamine Salt.**—A warm solution of 0.30 g (1.3 mmole) of *dl*-**13** in 3 ml of methanol was treated with 0.22 g (1.3 mmoles) of *l*-1-(1-naphthyl)ethylamine[12] and the resulting solution was concentrated to 1 ml, whereupon a crystalline solid separated. The mixture was cooled, diluted with 25 ml of ether, and filtered. The collected salt (0.50 g) was recrystallized from 35 ml of hot acetonitrile with cooling only to about 40° and collection of the needles which had separated; 0.24 g, mp 178–188°. Two further recrystallizations afforded 0.14 g of blades, mp 191.5–193.5°, and a fourth recrystallization gave 0.11 g of the desired *l*-acid–*l*-base, mp 192.5–194°, $[\alpha]^{25}D$ −51° (*c* 1, EtOH).

Anal. Calcd for $C_{28}H_{39}NO_3$: C, 76.26; H, 8.62; N, 3.42. Found: C, 76.4; H, 8.7; N, 3.4.

***d*-4-(4-Hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid *d*-1-(1-Naphthyl)ethylamine Salt.**—A warm solution of 16.2 g (0.068 mole) of *dl*-**13** in absolute ethanol was treated with 12.0 g (0.070 mole) of *l*-1-(1-naphthyl)ethylamine.[12] A crystalline precipitate formed shortly. Ether (400 ml) was added and the precipitate of crude *l*-acid–*l*-base (21.7 g) was collected. Three recrystallizations gave the pure salt as described in the preceding experiment.

The combined mother liquors from the operations just described were then rich in the *d*-acid salts. Concentration afforded 18.1 g of a solid residue which was treated with 200 ml of H_2O and 44 ml of 2 *N* NaOH. The liberated base was extracted with two portions of ether and the alkaline aqueous solution was then acidified with 2 *N* HCl. A precipitate formed which was collected, air-dried, and dissolved in 75 ml of absolute ethanol. Addition of 6.00 g of *d*-1-(1-naphthyl)ethylamine[12] caused precipitation of 10.0 g of the *d*-base salt of the *d*-acid, mp 186–192.5°. Dilution of the filtrate with 425 ml of ether precipitated a further 2.1 g of salt, mp 183–189° after softening at 174°. Recrystallization of this second crop of crystals from 275 ml of acetonitrile afforded 1.5 g of blades, mp 188–192°. The 1.5- and the 10-g samples combined (82% yield) were then recrystallized from acetonitrile to give thin blades of *d*-acid–*d*-base which melted at 192–194°, $[\alpha]^{25}D$ +54° (*c* 1, EtOH).

Anal. Calcd for $C_{28}H_{39}NO_3$: C, 76.26; H, 8.62; N, 3.42. Found: C, 76.1; H, 8.5; N, 3.5.

***l*-4-(4-Hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid (13).**—A 1.000-g sample of *l*-4-(4-hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexane-

(12) Sold as Resobine-A by the Research and Development Department, Rock Hill Laboratory, Newport, Tenn.

acetic acid *l*-1-(1-naphthyl)ethylamine salt was shaken with 20 ml of 1 *N* NaOH solution and 50 ml of ether. The water layer was separated and acidified. The theoretical amount of *l*-acid was precipitated (0.58 g), mp 187–192°. Recrystallization from ethyl acetate afforded 0.47 g of needle clusters (or heavy plates of an unstable polymorph which reverted to needles on standing), mp 193–194° and unchanged by further recrystallization, $[\alpha]^{25}D$ −77° (*c* 1, EtOH).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.31; neut equiv, 238.3. Found: C, 70.3; H, 9.4; neut equiv, 239.

***d*-4-(4-Hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetic acid** (**13**) was obtained from its *d*-1-(1-naphthyl)ethylamine salt in the manner just described for the *l*-acid. Eleven grams of the salt yielded 5.61 g (88%) of acid melting at 190–193°. Recrystallization from ethyl acetate afforded needle clusters or transient heavy plates which reverted to needles, mp 193–194°, $[\alpha]^{25}D$ +75° (*c* 1, EtOH).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.31; neut equiv, 238.3. Found: C, 70.8; H, 9.0; neut equiv, 236.

2-Dimethylaminoethyl *dl*-4-(4-hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetate (**14**) was prepared in the standard manner from 6 g of *dl*-acid **13**. The product from partition chromatography solidified. A single recrystallization from acetonitrile furnished an analytically pure sample (1.31 g, 17%), mp 97–98.5°.

Anal. Calcd for $C_{18}H_{31}NO_3$: C, 69.87; H, 10.10; N, 4.52. Found: C, 69.6; H, 9.8; N, 4.8.

The **hydrochloride salt** of ester **14** was recrystallized from isopropyl alcohol to give colorless needles, mp 234–235°.

Anal. Calcd for $C_{18}H_{31}NO_3 \cdot HCl$: C, 62.50; H, 9.33; Cl, 10.25. Found: C, 62.5; H, 9.4; Cl, 10.1.

The **dihydrogen phosphate salt,** recrystallized from absolute ethanol, formed plates, mp 178–188°, which were soluble to 10% in water in contrast to the <1% value for the hydrochloride salt.

Anal. Calcd for $C_{18}H_{31}NO_3 \cdot H_3PO_4$: N, 3.44; P, 7.60. Found: N, 3.4; P, 7.4.

Ethyl *dl*-4-(4-*t*-Butoxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetate (**15**).—A mixture of 6.00 g (0.0225 mole) of **12**, 150 ml of CH_2I_2, 1.50 ml of BF_3 etherate, 0.66 ml of 100% H_3PO_4, and 100 ml of isobutene was shaken vigorously in a closed vessel at room temperature for 4 hr. To this mixture were added 75 ml of 2 *N* NH_4OH, 7 ml of brine, and 100 ml of ether. The layers were separated and the organic layer was washed twice with brine and concentrated to a residue. This was chromatographed on 150 g of silica gel using 1:9 ether–pentane for elution to give 5.04 g of crude product. Elution with pure ether afforded 1.38 g (23%) of recovered starting material, mp 98–100°. Recrystallization of the product from methanol gave 4.92 g (68%) of title compound, mp 72–77°. One further recrystallization raised the melting point to 77–79°, λ_{max}^{EtOH} 222 mμ (ε 17,900).

Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.48; H, 10.63. Found: C, 74.4; H, 10.3.

***dl*-4-(4-*t*-Butoxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid** (**16**).—A solution of 3.54 g (0.011 mole) of **15** in 60 ml of 95% ethanol was treated with 10 ml of 2 *N* NaOH (0.020 mole) and allowed to stand overnight. Work-up in the standard manner afforded 1.37 g (39%) of recovered ester from the neutral fractions and 1.85 g of crude acid (**16**). Recrystallization from acetonitrile furnished 1.20 g (38%) of **16**, mp 188–190°.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.2; H, 10.2.

2-Dimethylaminoethyl *dl*-4-(4-*t*-butoxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetate (**17**) was prepared from 1.84 g of **16** in the standard manner; 60 g of Supercel was used for the partition chromatography. The product was converted to its **hydrochloride salt** which was recrystallized by dissolving it in methanol and precipitating it with ether. Warming this salt in methanolic solution caused cleavage of the butyl ether. The pure salt (0.50 g, 20%) melted at 231° dec.

Anal. Calcd for $C_{22}H_{39}NO_3 \cdot HCl$: C, 65.73; H, 10.03; N, 3.48. Found: C, 65.8; H, 10.1; N, 3.6.

Ethyl 4-(4-Hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetate Phenylurethan (**18**).—A mixture of 6.0 g (0.022 mole) of ethyl ester **12**, 2.58 g (0.022 mole) of phenyl isocyanate, and 30 ml of acetonitrile was heated under reflux for 7 hr. When the cooled mixture formed a pasty mass, it was diluted with enough water to render it a mobile slurry for filtration. The collected solid was recrystallized once from 60 ml of acetonitrile to give 5.68 g of title compound, mp 132–134°.

4-(4-Hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetic acid phenylurethan (**19**) was prepared from 0.75 g of the corresponding ethyl ester (**18**) by the standard procedure. The crude product was dissolved in 90 ml of acetonitrile, and the solution was concentrated to 20 ml and cooled to give 0.48 g (70%) of **19**, mp 203–207°.

Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.57; H, 7.61; neut equiv, 357.4. Found: C, 70.7; H, 7.7; neut equiv, 355.

2-Dimethylaminoethyl 4-(4-Hydroxycyclohexyl)-$\Delta^{1,\alpha}$-cyclohexaneacetate Phenylurethan (**20**).—A suspension of 7.60 g (0.021 mole) of **19** in 80 ml of $CHCl_3$ was treated with 30 ml of $SOCl_2$ dropwise with stirring and cooling. The mixture was stirred at room temperature until it became homogeneous (3 hr) and for 0.5 hr longer. The solution was concentrated to a residue at <35° under reduced pressure and 80 ml of $CHCl_3$ was added. 2-Dimethylaminoethanol (19 ml) was added dropwise with stirring and cooling and the mixture was boiled for 5 min. It was cooled and diluted with ether and dilute NH_4OH. The ether layer was washed twice with brine and concentrated to a residue which crystallized.

The crude basic ester was chromatographed on eight 20 × 40 cm silica-coated plates which were developed with 3:3:94 methanol–isopropylamine–$CHCl_3$. The material from the main band was recrystallized from acetonitrile to give 1.79 g (20%) of **20**, mp 107–108°.

Anal. Calcd for $C_{25}H_{36}N_2O_4$: C, 70.07; H, 8.46; N, 6.53. Found: C, 69.9; H, 8.2; N, 6.4.

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