Acknowledgment.—The author is grateful to W. E. Wright for valuable discussions; to G. Maciak and his staff for the microanalyses; to H. Boaz, D. O. Woolf, L. A. Spangle, and their associates for spectral data and titrations; to W. E. Wick and J. L. Ott for biological data; to C. T. Pugh for bioautography; and to A. I. Ellis for technical assistance.

Cassaine Analogs. V.[1] A Distant Analog of Cassaine

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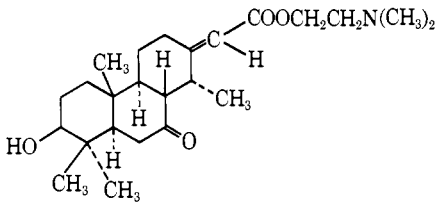
Extending our efforts in the search for a cardiac stimulant, we have prepared another analog related to the *Erythrophleum* alkaloid cassaine (**1**).[2] We felt



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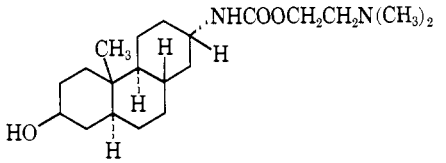
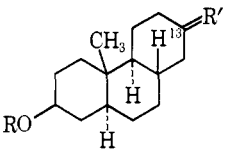
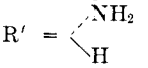
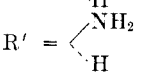
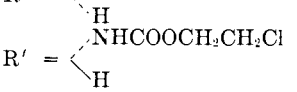
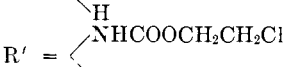
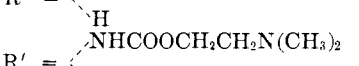


2

that if the group $=CHCOOCH_2CH_2N(CH_3)_2$ of **1** were replaced by the equatorially oriented $-NHCOOCH_2CH_2N(CH_3)_2$, perhaps we could obtain a cardiac stimulant having a much longer duration of activity. The ease of *in vivo* hydrolysis of the ester group might be related to duration of activity. It was hoped that the equatorial configuration of the side chain would approximate the configuration demanded by the double bond of the natural product and that the unshared electron pair on the nitrogen might substitute for the electron character of the double bond. In order to test this hypothesis, we have prepared the carbamate **2**.

The hydroxyl group of the starting material **3** was protected as its *t*-butyl ether derivative **4**[3] while the necessary transformations were made at C-13. The oxime **5** of **4** was reduced chemically (Na, EtOH), a procedure which allows assignment of the major product as the equatorial (α) amine **6** and the minor product as the axial (β) amine **7**. Not being crystalline, these amines were characterized by their conversion in the next step of the sequence to crystalline 2-



3, R = H; R′ = O
4, R = *t*-C_4H_9; R′ = O
5, R = *t*-C_4H_9; R′ = NOH
6, R = *t*-C_4H_9; R′ = 
7, R = *t*-C_4H_9; R′ = 
8, R = *t*-C_4H_9; R′ = 
9, R = *t*-C_4H_9; R′ = 
10, R = *t*-C_4H_9; R′ = 
11, R = F_3CCO; R′ = 

chloroethyl carbamates **8** and **9**. Reaction of **8** with dimethylamine afforded the dimethylaminoethyl carbamate **10** which was characterized as its hydrochloride salt. The *t*-butyl ether group in **10** was cleaved by treatment with trifluoroacetic acid; the compound isolated was the trifluoroacetate **11**. This ester was hydrolyzed with methanolic NH_4OH at room temperature to give 2-dimethylaminoethyl *dl*-N-(1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-tetradecahydro-7β-hydroxy-4bβ-methylphenanthr-2α-yl)carbamate (**2**) in good yield.

Biological Testing.[4]—Compound **2**, upon intravenous administration in the dog at a dose level of 4 mg/kg, produced an increase of 30% in ventricular contractile force, accompanied by a blood pressure drop of 25%.[5] Ouabain at a dose level of 0.03 mg/kg or cassaine (**1**) at a dose level of 0.04 mg/kg produces an increase in ventricular contractile force of 20% without concomitant lowering of blood pressure.[4]

Experimental Section[6]

***dl*-7β-*t*-Butoxy-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-dodecahydro-4bβ-methyl-2(1H)-phenanthrone 2-Oxime (5).**—A solution of 6 g (25 mmoles) of hydroxyphenanthrone **3**[7] in 150 ml of CH_2Cl_2 was treated with 1 ml of BF_3 etherate and 1 ml of anhydrous H_3PO_4. The latter was prepared by the addition of a calculated amount of P_2O_5 to 85% H_3PO_4. Isobutene (150 ml) was added to the solution at 10°. The solution was shaken in the Parr shaker for 5 hr. The reaction mixture was poured into 200 ml of 2 *N* NH_4OH, the layers were separated, and the aqueous layer was washed with 200 ml of CH_2Cl_2. The organic layers were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield an oil that was chromatographed on 300 g of silica gel. Ether eluted 4.7 g of ***dl*-7β-*t*-butoxy-3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-dodecahydro-4bβ-methyl-2(1H)-phenanthrone** (**4**) as an oil that would not crystallize. The oil,

(1) For paper IV see 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**, 593 (1967).
(2) See F. Erjavec and Š. Adamic, *Arch. Intern. Pharmacodyn.*, **155**, 251 (1965); E. L. McCawley, *Alkaloids*, **5**, 101 (1955), and references therein.
(3) H. C. Bayerman and G. J. Heiszwolf, *Rec. Trav. Chim.*, **84**, 203 (1965).
(4) For details of the experimental methods of evaluation see 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).
(5) We wish to thank Mr. William V. O'Connor for the biological testing.
(6) All melting points are corrected. Ir spectra were recorded on a Perkin-Elmer Infrared spectrophotometer, Model 21. The silica gel used for column chromatography (100–200 mesh) was obtained from the Davison Co., Baltimore, Md. Silica gel G, purchased from Brinkmann Instruments, Inc., was used for thin layer chromatography. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.
(7) S. J. Daum, P. E. Shaw, and R. L. Clarke, *J. Org. Chem.*, **32**, 1427 (1967).

in 25 ml of EtOH, was added to 2.8 g (40 mmoles) of $HONH_2 \cdot HCl$ in 50 ml of EtOH containing 15 ml of pyridine. The reaction mixture was refluxed for 2 hr and then left at room temperature overnight. Dilution with a large volume of H_2O and filtration gave 4.52 g of the title compound **5** (59%), mp 154–156°, λ_{max}^{KBr} 3.10 (OH) and 6.17 μ (w, >C=N). The analytical sample (from MeOH) melted at 160–161°. *Anal.* ($C_{19}H_{33}NO_2$) C, H, N.

***dl*-7β-*t*-Butoxy-1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10aβ-tetradecahydro-4bβ-methylphenanthryl-2α- and -2β-amines (6 and 7).**—A solution of 9.4 g (0.029 mole) of the oxime **5** in 70 ml of absolute EtOH was heated under reflux while 10 g (0.44 g-atom) of Na was added portionwise over a 2.5-hr period. At the end of this time more EtOH and some ice water were added. The mixture was extracted (Et_2O) and the ether was washed (saturated NaCl). The aqueous layers were washed with another portion of ether. The combined ether layers were dried (Na_2SO_4) and the solvent was removed by warming *in vacuo* to afford 10 g of an oil. The oil was chromatographed on 1 kg of silica gel using Et_2O–pentane–MeOH–*i*-$PrNH_2$ (50:44:3:3) for elution. Fractions were combined on the basis of tlc analysis. The main fraction afforded 7.2 g of a mixture of amines.

Partial separation of the isomers was obtained by using a method of partition chromatography described by Brown and Kupchan.[8] The solvent system employed was a 12:1:2:0.2 mixture of hexane–$(ClCH_2)_2$–MeOH–H_2O. Supercel (400 g) was wetted with 300 ml of the polar phase containing 100 mg of bromocresol purple, the color of the indicator 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. A sample of the mixture of amines (6.7 g) was dispersed on approximately 50 g of Supercel and placed on top of the column. Elution of the column with the nonpolar phase of the solvent mixture developed the column; the position of the basic amines was revealed by two bands.

The more polar band was obtained by slicing the column and eluting the component with Et_2O-*i*-$PrNH_2$, (20:1). The oil obtained (2.3 g) gave a major single spot with an R_f of 0.19 and a trace of impurity at R_f 0.31 (silica gel, Et_2O–MeOH–*i*-$PrNH_2$, 94:3:3). The less polar band afforded 4.2 g of oil which was a mixture of the two amines by tlc. The latter material was chromatographed again on 14 silica gel coated plates (Brinkmann PF_{254} silica gel, 20 × 40 cm) having a 1-mm coating. The plates were developed with Et_2O–*i*-$PrNH_2$–MeOH, (94:3:3). The major more polar band afforded another 3.3 g of oil having a single spot by tlc identical with the material of R_f 0.19. The less polar material afforded 0.4 g of product having a major spot on a tlc analysis (silica gel, Et_2O–MeOH–*i*-$PrNH_2$, 94:3:3) at R_f 0.31 with a trace at R_f 0.19.

Structure **6** was assigned to the material of R_f 0.19 (62%) and **7** to the material at R_f 0.31 (4.5%). These amines could not be crystallized.

2-Chloroethyl *dl*-N-(7β-*t*-Butoxy-1,2,3,4,4aα,4b,5,6,7,8,8aα,-9,10,10aβ-tetradecahydro-4bβ methylphenanthr-2α-yl)carbamate (8).—The amine **6** (4.4 g, 15 mmoles) was suspended in 50 ml of ice-water. While the flask was being swirled in an ice bath, 4 g (28 mmoles) of chloroethyl chloroformate was added portionwise. When half of the reagent had been added, 10 ml of 2 *N* NaOH was added to the reaction mixture followed by the remainder of the chloroethyl chloroformate. More 2 *N* NaOH (10 ml) was added. The reaction mixture was swirled occasionally for another 15–30 min while in the ice bath. The oily contents of the flask solidified and were filtered. The solid residue was dissolved in ether. The ether solution was washed (dilute HCl, saturated NaCl) and dried (Na_2SO_4). Concentration of the solvent *in vacuo*, filtration, and recrystallization of the precipitate afforded 2.8 g (47%) of **8**. The analytical sample (from Et_2O) melted at 153–154°. A similar sample had λ_{max}^{KBr} 3.05 (ms) and 6.50 (NH), 5.94 μ (s) (>C=O). *Anal.* ($C_{22}H_{38}ClNO_3$) C, H, Cl.

2-Chloroethyl *dl*-N-(7β-*t*-Butoxy-1,2,3,4,4aα,4b,5,6,7,8,8aα,-9,10,10aβ-tetradecahydro-4bβ-methylphenanthr-2β-yl)carbamate (9).—In a procedure similar to that used in the above experiment, 0.4 g (1.3 mmoles) of amine **7** afforded 0.4 g (73%) of **9**, mp 132–134°. The analytical sample from cyclohexane melted at 134–135°. *Anal.* ($C_{22}H_{38}ClNO_3$) C, H, N.

2-Dimethylaminoethyl *dl*-N-(7β-*t*-Butoxy-1,2,3,4,4aα,4b,5,6,-7,8,8aα,9,10,10aβ-tetradecahydro-4bβ-methylphenanthr-2α-yl)-carbamate (10).—A solution of 2.42 g (6.0 mmoles) of **8** in 80 ml of Me_2NH was heated in a sealed glass tube on a steam bath for 24 hr. The tube was cooled and opened and the excess Me_2NH was evaporated. Ether and 2 *N* NaOH were added and the layers were separated. The ether was washed with saturated NaCl. The aqueous layers were washed again with a portion of ether. The combined ether layers were dried (Na_2SO_4) and the solvent was removed by warming *in vacuo* to afford **10**. In the usual manner, 2.17 g (81%) of crude hydrochloride salt was obtained, mp 115–125° (gelatinous melt). Two recrystallizations from acetone–ether afforded 1.58 g of **10 hydrochloride**, mp 150–180°. *Anal.* ($C_{24}H_{44}N_2O_3 \cdot HCl$) C, H, N.

2-Dimethylaminoethyl *dl*-N-(1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,-10aβ-Tetradecahydro-7β-hydroxy-4bβ-methylphenanthr-2α-yl)-carbamate 7-Trifluoroacetate (11).—A solution of 1.3 g (3.1 mmoles) of **10** (free base) in 18 ml of CF_3CO_2H stood in an ice bath for 2.5 hr. The solvent was removed at 40° (maximum). CH_2Cl_2 and saturated $NaHCO_3$ were added. The layers were separated and the organic phase was washed with saturated NaCl and dried (Na_2SO_4), and the solvent was removed *in vacuo*. Recrystallization of the residue from ether and then from acetone afforded 0.85 g (61%) of **11**, mp 195–197°. The analytical sample from acetone melted at 199–200°. *Anal.* ($C_{32}H_{51}F_3N_2O_4$) N, F, N_{AE}.

2-Dimethylaminoethyl *dl*-N-(1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,-10aβ-Tetradecahydro-7β-hydroxy-4bβ-methylphenanthr-2α-yl)-carbamate (2).—Compound **11** (680 mg, 1.5 mmoles) in 50 ml of MeOH containing 10 ml of concentrated NH_4OH sat at room temperature for 1 hr. The mixture was poured into some ice and the aqueous mixture was extracted with ether. The ether was washed with saturated NaCl. The aqueous layers were washed with a fresh portion of ether. The combined ether layers were dried (Na_2SO_4). Concentration *in vacuo* afforded 400 mg of **2** (87%), mp 133–134°. The analytical sample obtained from ether melted at 134–135°. *Anal.* ($C_{29}H_{46}N_2O_3$) C, H, N.

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

Silicon-Substituted Medicinal Agents. Parasympatholytic Activity of 3,3-Dimethyl-1-butanol Carbamate and 2-Trimethylsilyl-1-ethanol Carbamate[1]

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In a previous study[3] it was observed that 3,3-dimethyl-1-butanol carbamate (**1**) was a convulsant and ten times more toxic than its silicon isostere, 2-trimethylsilyl-1-ethanol carbamate (**2**), a muscle relaxant at high doses.

$(CH_3)_3CCH_2CH_2OCONH_2$ (**1**) $\quad (CH_3)_3SiCH_2CH_2OCONH_2$ (**2**)

$(CH_3)_3NCH_2CH_2OCONH_2$ (**3**)

Both **1** and **2** are similar in structure to carbachol (**3**), and it was of interest to determine if these compounds would elicit a muscarinic response in a guinea pig ileum assay.

After standardization of the test conditions (see Experimental Section), **1** and **2** were assayed and found to be void of muscarinic activity. However, both compounds were found to be antagonists of the muscarinic

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(2) (a) Alfred P. Sloan Fellow, 1965–1969. (b) To whom inquiries should be addressed: Department of Chemistry, University of Montana, Missoula, Montana 59801.

(3) R. J. Fessenden and M. D. Conn, *J. Med. Chem.*, **8**, 604 (1965).