matographed on silica gel. Elution with a 30% hexane–70% toluene solvent mixture afforded 5.2 g (55%) of product, mp 41.0–42.0 °C (lit.[8] mp 41 °C).

Radioligand Binding. Assays for the competitive binding of selected compounds to central α-adrenergic binding sites employed radiolabeled clonidine or radiolabeled prazosin, which were obtained from New England Nuclear and Amersham, respectively. [^{3}H]Clonidine (specific activity 22.2–23.8 Ci/mmol) was stored in EtOH–H_2O (7:2) at 0 °C, and [^{3}H]prazosin (specific activity 33 Ci/mmol) was stored in a solution of 1% EtNH in EtOH at 0 °C. The radiochemical purity of these ligands was periodically checked by TLC.

Binding assays were conducted by using frozen sections of calf cerebral cortex (–70 °C). A Brinkmann Polytron PT-10, at setting 6 for 10 s, was used to homogenize the frozen tissue in 20 vol (w/v) of ice-cold 50 nM pH 7.7 Tris-HCl buffer. The resultant homogenate was centrifuged twice at 48000*g* (Sorvall SS-34 rotor, 2000 rpm, RC-5 centrifuge) for 10 min at 40 °C, with rehomogenization of the intermediate pellet in 20 vol of fresh buffer. This final pellet was resuspended in 50 vol of ice-cold buffer.

Standard displacement assays were run with either 0.20 nM [^{3}H]clonidine or 0.14 nM [^{3}H]prazosin. Triplicate assay tubes contained ^{3}H-labeled ligand, 100 μL of various concentrations of the compound being investigated, 1 mL of tissue homogenate, and 50 mM pH 7.7 Tris-HCl buffer to a final volume of 2 mL. The reaction was initiated by the addition of tissue, and incubation continued for 30 min at 25 °C, at which time it was terminated by rapid filtration through Whatman GF/B glass-fiber filters under vacuum. Each filter was immediately rinsed with 3 × 5 mL aliquots of ice-cold buffer. The filters were removed into 10 mL of PCS (Amersham) and counted on either a Packard Model 2425 or Packard Model 460C scintillation spectrophotometer at approximately 35% efficiency.

Specific binding was defined as the difference between samples with and without 1 μM clonidine or 1 μM prazosin for [^{3}H]clonidine and [^{3}H]prazosin assays, respectively.

Data from binding assays were plotted as log concentration vs. percent inhibition and analyzed by nonlinear least-squares techniques in which 100% maximal inhibition was assumed at high test compound concentrations. The IC_{50} values obtained from such data treatment were used to calculate apparent inhibition constants from eq 1, where [C] is the concentration of

$$K_i = \frac{IC_{50}}{1 + ([C]/K_D)} \quad (1)$$

radioligand employed in the binding assay, and K_D is its receptor dissociation constant (K_D = 0.48 nM for [^{3}H]clonidine and 0.14 nM for [^{3}H]prazosin).

Rat Vas Deferens. Vas deferens were extirpated from Sprague–Dawley rats (250–350 g) and prepared for field stimulation as described previously.[7] Agonist EC_{50} values plus or minus 95% confidence limits were determined by regression analyses of cumulative dose–response curves ($N \geq 2$ tissues) as previously described.[7] α_2-Adrenergic agonist activity was determined by pretreating the tissues with prazosin (78 nM). The α_1- and α_2-adrenergic agonist activity of the test compounds was verified by the ability of prazosin (78 nM) and rauwolscine (280 nM) to completely reverse the contractile enhancement or inhibition, respectively, produced by the test compounds.

Antagonist pA_2 values were estimated on the basis of one or two concentrations of the test compounds using a minimum of three tissues at each concentration.[9] Clonidine and methoxamine were used as α_2- and α_1-adrenergic agonists, respectively, according to the protocols described by Lotti et al.[7]

Acknowledgment. The authors are indebted to Y. Lee and J. Moreau for elemental analyses, P. Bennett, E. Cresson, T. Lyon, and M. Zrada for receptor-binding determinations, J. Murphy for ^{1}H NMR spectra, and D. Cerino and P. Kling for technical assistance with the vas deferens assay. We also thank M. Banker for preparation of the manuscript.

Registry No. **4a**, 87261-69-6; **4a**·HCl, 87261-62-9; **4b**, 87261-70-9; **4b**·HCl, 87261-63-0; **4c**, 87261-71-0; **4c**·2HCl, 87261-64-1; **4d**, 87261-72-1; **4d**·2HCl, 87261-65-2; **4e**, 87261-73-2; 4e·HCl, 87261-66-3; **4f**, 87261-67-4; **4f** difumarate, 87261-68-5; **4g**, 87261-74-3; **4g**·HCl, 67084-31-5; 2-(chloromethyl)-4,5-dihydro-1*H*-imidazole hydrochloride, 13338-49-3; *N*-cyclohexyl-4-methylaniline, 10386-93-3; 3-hydroxyaniline, 591-27-5; *p*-toluidine, 106-49-0; cyclohexanone, 108-94-1.

(8) Miller, T. G. *J. Org. Chem.* **1966**, *31* 3178.

(9) Mackay, D. *J. Pharm. Pharmacol.* **1978**, *30*, 312.

Parasympatholytic (Anticholinergic) Esters of the Isomeric 2-Tropanols. 2. Non-Glycolates

Edward R. Atkinson,*[†] Donna D. McRitchie-Ticknor,[†] Louis S. Harris,[‡1] Sydney Archer,[‡2] Mario D. Aceto,[‡1] J. Pearl,[‡] and F. P. Luduena[‡]

Arthur D. Little, Inc., Cambridge, Massachusetts 02140, and Sterling-Winthrop Research Institute, Rensselaer, New York 12144. *Received March 31, 1983*

The 19 esters in Table I were prepared from (+)-2α-tropanol, (–)-2β-tropanol, (±)-3-quinuclidinol, and a variety of non-glycolic acids in order to compare their central and peripheral activities with those of the glycolates reported in the previous paper. The results (Table II) showed that esters **6** and **17** were approximately equivalent to one another and to atropine, that **8** was equal in both central and peripheral activity to reference glycolates, that **9** and **19** were less active than **8** but **9** had a substantially reduced central activity, and that **10** and **11** were more active than the methoxy analogue reported earlier.

All the natural and many of the synthetic anticholinergic drugs (such as methixene and methantheline) are not glycolates. Some of these (such as scopolamine) have potent CNS activity. It was shown previously[3] that some glycolate esters of the 2-tropanol isomers **1** and **2** have powerful CNS effects. It was therefore of interest to de-

† Arthur D. Little, Inc.
‡ Sterling-Winthrop.
* Corresponding address: 163 Gray St., Amherst, MA 01002.

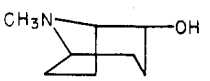
(1) Present address: Department of Pharmacology, Medical College of Virginia, Richmond, VA 23298.
(2) Present address: Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12181.
(3) Atkinson, E. R.; McRitchie, D. D.; Shoer, L. F.; Harris, L. S.; Archer, S.; Aceto, M. D.; Pearl, J.; Luduena, F. P. *J. Med. Chem.* **1977**, *20*, 1612.

0022-2623/83/1826-1772$01.50/0

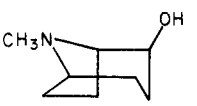
Table I. Esters of 2-Tropanols and of (±)-3-Quinuclidinol[a]

compd	alcohol	acid	formula	mp or bp (mm), °C	$[\alpha]_D$,[b] deg
1	(+)-2α-tropanol	3,3-diphenylhydracrylic	$C_{23}H_{27}NO_3$	122–124	+29.7
2		2,2-diphenylpentanoic	$C_{25}H_{31}NO_2$	gum	+12.0
3		chromone-2-carboxylic	$C_{18}H_{19}NO_4$	120–122	+20.6
4		3,4,5-trimethoxybenzoic	$C_{18}H_{25}NO_5$	57–58	+18.3
5		1-azaphenothiazine-10-carboxylic	$C_{20}H_{21}N_3O_2S$	125–128	+11.3
6		(±)-tropic	$C_{17}H_{23}NO_3$	74–100	+24.0
7		10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-carboxylic	$C_{24}H_{27}NO_2$	107–108	+4.3
8		chlorodiphenylacetic	$C_{22}H_{24}ClNO_2 \cdot HCl$	178–179 dec	+2.5
9[c]		diphenylfluoroacetic	$C_{22}H_{24}FNO_2$	73–74	+12.4
10		(benzyloxy)diphenylacetic	$C_{29}H_{31}NO_3 \cdot HCl$	201–203 dec	+4.0[d]
11[e]		diphenyl-*n*-propoxyacetic	$C_{25}H_{31}NO_3$	oil	+15.0
12		adamantoic	$C_{19}H_{29}NO_2$	117–119	+33.0
13	(−)-2β-tropanol	3,4,5-trimethoxybenzoic	$C_{18}H_{25}NO_5$	oil	+21.0
14		10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-carboxylic	$C_{24}H_{27}NO_2$	200–206 (0.2)	−26.2
15	(±)-3-quinuclidinol	2,2-diphenylpentanoic	$C_{24}H_{29}NO_2$	70–72	
16[f]		3,4,5-trimethoxybenzoic	$C_{17}H_{23}NO_5$	80–82	
17		(±)-tropic	$C_{16}H_{21}NO_3$	91–94	
18[g]		10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-carboxylic	$C_{23}H_{25}NO_2$	108–109	
19[c]		diphenylfluoroacetic	$C_{21}H_{22}FNO_2$	59–61	

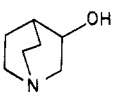
[a] With the exception of compounds 9, 18, and 19, all compounds in the table are novel. Pharmacologically equivalent salts have been reported for 11 and 16 as noted. [b] Unless otherwise noted, rotations were observed in 1-dm tubes at ambient temperatures in dry CH_2Cl_2 at 2% concentrations. [c] Papanastassiou, Z. B.; Atkinson, E. R.; McRitchie, D. D. U.S. Patent 3 833 592, 1974 (filed 1966); *Chem. Abstr.* 1974, *81*, 152030, and the indexes of Vol. *81* incorrectly omitted compound 9. [d] In MeOH. [e] For tosylate, mp 163.6–165.8 °C; see ref 6. [f] 16·HCl; mp 210–213; lit. mp 203–205 °C (Mikhlina, E. E.; Rubtsov, M. V. *Zh. Obshch. Khim.* 1960, *30*, 163); lit. mp 214–216 °C. (Judd, C. I. U.S. Patent 3 405 134, 1968). [g] Literature mp 102–104 °C (van der Stett, C. *Recl. Trav. Chim. Pays-Bas* 1965, *84*, 1466).



1, (+)-2α-tropanol



2, (−)-2β-tropanol



3, (±)-3-quinuclidinol

termine whether non-glycolate esters of these alcohols are active.

The 14 esters of 2-tropanol isomers shown in Table I were prepared from acids well-known in medicinal chemistry and pharmacology. Five of these acids were also converted into esters of (±)-3-quinuclidinol (**3**) in order to extend the comparison between the 2-tropanol and 3-quinuclidinol series previously made for glycolates.

Pharmacology. The data in Table II were collected by the same test protocols used previously.[3] When mydriasis ED_{50} values showed a compound to be relatively inactive, the anti-tremorine ND values were not determined. Esters of (−)-2α-tropanol and (+)-2β-tropanol were not examined because these two isomers were difficult to prepare, and no outstanding activity had been observed with their glycolates.

The data in Table II support the following conclusions. (1) The (±)-tropate esters **6** and **17** are approximately equivalent to one another and to the reference compound atropine. Compound **17** has previously been obtained as an impure mixture with the atropate ester.[4] (2) Compound **8** is equal in both peripheral and central activity to (+)-2α-tropanyl benzilate reported previously. The activity is ascribed to the easy hydrolysis of the chlorine atom, a reaction that has been observed by us and also with other esters of the chloro acid.[5] (3) Compounds **9** and **19** have approximately equal peripheral activity. Both are less active than **8**, presumably because the fluorine atom is more resistant to hydrolysis. In addition, compound **9** has a substantially reduced CNS activity. (4) Compound **11**, which is still less active, is significantly more active than the benzyloxy compound **10**. Both **10** and **11** are more active in both peripheral and central nervous systems than the methoxy homologue.[6] The unusually high central/peripheral activity ratios reported for the 3α-tropanyl esters of these alkoxy acids[7] were probably peculiar to the test systems used. Other aminoalkyl esters of the alkoxydiarylacetic acids have been investigated extensively as analgesics, spasmolytics, and sedatives by many investigators.[8] (5) The remaining compounds are relatively inactive; comparisons among them are not warranted. They were not examined for pharmacological properties other than those in Table II. Other reported pharmacology on analogues of these compounds is extensive.

The *p*-nitrophenylacetate and *p*-tolylacetate esters of 2α-tropanol were reported to be less toxic than the 3α-tropanyl analogues.[9] No other non-glycolates of the 2-tropanols have been reported.

Chemistry. Compounds **2**, **4**, **7**, **10–16**, and **18** were prepared by the smaller-scale transesterification process described previously.[3] For **2**, the reaction required 7.5 h, and the crude product contained some 2β-tropanyl ester

(4) Sternbach, L. H.; Kaiser, S. *J. Am. Chem. Soc.* **1952**, *74*, 2219.

(5) King, F. E.; Holmes, D. *J. Chem. Soc.* **1947**, 164.
(6) Archer, S.; Bell, M. R. U.S. Patent 3 145 210, 1964.
(7) Farquharson, M. E.; Johnston, R. G. *Br. J. Pharmacol. Chem.* **1959**, *14*, 559.
(8) See, for example: Klosa, J.; *J. Prakt. Chem.* **1964**, *26*, 32. Doyle, F. P.; Mehta, M. D.; Ward, R.; Bainbridge, J.; Brown, D. M. *J. Med. Chem.* **1965**, *8*, 571.
(9) Friess, S. L.; Fash, F. J.; Kelly, H. V.; Martin, H. L.; Polaski, P. M. *Toxicol. Appl. Pharmacol.* **1965**, *7*, 794.

Table II. Peripheral and Central Effects of 2-Tropanyl and (±)-3-Quinuclidinyl Esters

compd in Table I	mydriasis: ED_{50}, mg/kg, sc (mouse)	anti-tremorine: ND, mg/kg, sc (mouse)	LD_{50}, mg/kg, iv (mouse) (fiducial limits)
1	>10		18.0 (5.6-56)
2	>10		18.0 (5.6-56)
3	>10		100 (32-320)
4	32		56 (18-180)
5	5.6		32 (10-100)
6	0.1		50 (40-63)
7	5.6		32 (10-100)
8	0.03[a]	0.045[a]	22[a] (18-28)
9	0.25	0.68	36 (25-50)
10	5.6[a]	6.0[a]	56[a] (18-180)
11	0.94	0.72	22 (18-28)
12	>10		32 (10-100)
13	>10		18 (5.6-56)
14	>10		18 (5.6-56)
15	>10		18 (5.6-56)
16	>10		18 (5.6-56)
17	0.08	>2	45 (36-56)
18	1.8	4.1	28 (22-36)
19	0.22	0.20	22 (18-28)
atropine	0.061	2.2	32 (10-100)
scopolamine	0.012	1.3	100 (32-316)
(+)-2α-tropanyl benzilate	0.05	0.03	14 (12-18)
(±)-3-quinuclidinyl benzilate	0.05	0.16	25 (20-32)

[a] Dose calculated as the free base.

(TLC and NMR); this was removed by extraction of **2** into hexane from a solution of the crude product in MeOH/H_2O (1:1) in which the 2β-isomer remained dissolved. Compound **2**, obtained by evaporation of the hexane extract, retained minor impurities and could not be obtained in crystalline form. For **15**, the reaction was similarly slow. Compound **13** could not be crystallized, nor was a nicely crystalline salt obtained. The crude product retained one molecule of H_2O per molecule of ester, a behavior typical of other 2β-tropanyl esters. Anhydrous **13** was obtained after the hydrate stood over $CaSO_4$ for 1 month. Similar behavior was observed with **14**; it was purified by short-path vacuum distillation. Compound **10** was isolated as the HCl salt from EtOAc when the free base could not be crystallized. Although **11** has previously[6] been obtained as a tosylate, neither this nor a HCl salt could be obtained in analytical purity. The oily free base **11** was homogeneous by TLC after drying at 0.05 mm for 20 h.

A transesterification between (+)-2α-tropanol and ethyl 3,3-diphenylhydracrylate[10] gave benzophenone as the principal product. A procedure analogous to that described[11] for the condensation of ethyl acetate with benzophenone, said to be superior to that of a conventional Reformatsky reaction, was then used for the preparation of compound **1**.

Attempts to esterify (+)-2α-tropanol and (±)-3-quinuclidinol by transesterification with the ethyl[12] and methyl[13] esters of chromone-2-carboxylic acid gave only the acid. (+)-2α-Tropanol was then converted to **3** in good yield by use of chromone-2-carbonyl chloride in a procedure similar to that used for the preparation of the 3α-tropanyl ester.[14] Saponification of a portion of **3** gave (+)-2α-tropanol of high optical purity, showing that no significant racemization occurred under the acid reaction conditions.

Transesterification of (+)-2α-tropanol with methyl tropate to **6** was slow and the product contained excessive atropate ester. When the tetrahydropyranyl ether of methyl tropate was used, transesterification with the tropanol was too slow.

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, and by the late Dr. S. M. Nagy, Belmont, MA. All the compounds in Table I gave analytical values within 0.4% of theory for C, H, N, and, where pertinent, S, and Cl. Satisfactory IR, UV, and NMR spectra were recorded for all novel compounds in this work. No attempt was made to optimize yields. The TLC system used silica plates and development by 5% methanol in hexane.

(+)-2α-Tropanyl 3,3-Diphenylhydracrylate (1). A solution of lithium amide in liquid ammonia was prepared by adding 0.45 g (0.06 mol) of lithium wire and a crystal of ferric nitrate to 80 mL of ammonia and stirring until the blue color faded. To this solution was added, in a single portion, a solution of 5.5 g (0.03 mol) of benzophenone and 5.5 g (0.03 mol) of 2α-tropanyl acetate[15] in a little ether. The mixture was stirred for 1 h, during which several color changes were observed. Solid ammonium chloride (3.2 g, 0.06 mol) was stirred in, and then the ammonia was allowed to evaporate. The crude solid residue was recrystallized from hexane to yield 4.5 g of pure **1**. When 2α-tropanyl acetate and benzophenone were added consecutively to the lithium amide solution, the desired condensation did not occur. This phenomenon had been reported with the ethyl acetate–benzophenone model reaction.

(+)-2α-Tropanyl 1-Azaphenothiazine-10-carboxylate (5). A mixture of 5.6 g (0.04 mol) of 2α-tropanol, 5.3 g (0.02 mol) of 1-azaphenothiazine-10-carbonyl chloride,[16] and 75 mL of ethylene chloride was refluxed for 21 h, during which 2.2 g of 2α-tropanol hydrochloride separated. It was filtered from the cooled suspension, and 5 g of gummy ester was isolated by evaporation of the filtrate. After treatment with decolorizing carbon in MeOH, the gum was again isolated and then extracted with 3 × 150 mL of boiling hexane, each portion containing 1 mL of MeOH. The

(10) Kurihara, T.; Chiba, K.; Kameyama, T. *Annu. Rep. Tohoku Coll. Pharm.* **1955**, *no. 2*, 42; *Chem. Abstr.* **1956**, *50*, 10688.
(11) Dunnavant, W. R.; Hauser, C. R. *J. Org. Chem.* **1960**, *25*, 503.
(12) Vejdelek, Z. J.; Trcka, V.; Chyba, O.; Chybova, H. *Chem. Listy* **1953**, *47*, 575; *Chem. Abstr.* **1955**, *49*, 306.
(13) Schmutz, J.; Lauener, H.; Hirt, R.; Sanz, M. *Helv. Chim. Acta* **1951**, *34*, 767.
(14) DeVries, J. X.; Vidal-Beretervide, K. *Nature (London)* **1961**, *191*, 171.
(15) Archer, S.; Lewis, T. R.; Bell, M. R.; Schulenberg, J. W. *J. Am. Chem. Soc.* **1961**, *83*, 2386.
(16) Schuler, W. A.; Klebe, H.; von Schlichtegroll, A. *Justus Liebigs Ann. Chem.* **1964**, *673*, 102.

extracts were evaporated to dryness, and the residue was recrystallized from hexane to yield 4.1 g of **5**.

(+)-2α-**Tropanyl** (±)-**Tropate** (**6**). A mixture of 5.3 g (0.03 mol) of 2α-tropanol hydrochloride and 12.2 g (0.054 mol) of freshly prepared *O*-acetyltropoyl chloride[17] was stirred at 90–95 °C for 2.5 h and became homogeneous. The mixture was heated on a steam bath for 30 min with 60 mL of H_2O to remove the acetyl group. A small amount of unreacted oil was removed by extraction into ether. The aqueous phase was made basic and extracted with CH_2Cl_2. The extract was evaporated to give 4.5 g of an oil whose NMR spectrum indicated the presence of both tropate and atropate (sharp doublets at 5.88 and 6.34 ppm) esters.

The desired tropate was recovered by repeated leaching of the oil with hexane at room temperature until just 0.5 g remained undissolved. The combined leachings were stored for 5 days at 0 °C, during which 1.2 g of a solid, mp 74–100 °C, separated. NMR showed the absence of atropate. The N-CH_3 absorption showed sharp singlets at 2.24 and 2.29 ppm, indicating the presence of approximately equal amounts of the two expected diastereoisomers.

(+)-2α-**Tropanyl Chlorodiphenylacetate Hydrochloride** (**8**). A mixture of 5.6 g (0.04 mol) of 2α-tropanol, 13.8 g (0.05 mol) of chlorodiphenylacetyl chloride, 4.1 g (0.05 mol) of pyridine, and 50 mL of $CHCl_3$ was stirred at room temperature for 3 days, during which it became homogeneous. It was worked up in the usual way to yield 12 g of a hexane-soluble oil that could not be crystallized. The hydrochloride was prepared in ether and then leached with 500 mL of boiling EtOAc: yield 7 g. When a solution of the salt in water was warmed on a steam bath for just 10 min, the compound was hydrolyzed to (±)-2α-tropanyl benzilate.

(±)-**3-Quinuclidinyl** (±)-**Tropate** (**17**). A mixture of 6.5 g (0.04 mol) of 3-quinuclidinol hydrochloride and 15.8 g (0.07 mol) of freshly prepared *O*-acetyltropoyl chloride was treated exactly as described above for the preparation of compound **6**. In the present case, the 8.5 g of crude oily product contained no atropate ester. The oil was leached with several portions of boiling hexane, from which pure material crystallized on partial evaporation and cooling. The product was optically inactive, and the tropic acid obtained on hydrolysis was racemic.

Registry No. 1, 87395-51-5; **2**, 87395-52-6; **3**, 87395-53-7; **4**, 87395-54-8; **5**, 87395-55-9; **6** (isomer 1), 87421-55-4; **6** (isomer 2), 87479-98-9; **7**, 87395-56-0; **8**, 87395-57-1; **8**·HCl, 87421-56-5; **9**, 87421-57-6; **10**, 87395-58-2; **10**·HCl, 87421-58-7; **11**, 87395-59-3; **12**, 87395-60-6; **13**, 87421-59-8; **14**, 87421-60-1; **15**, 87395-61-7; **16**, 87395-62-8; **16**·HCl, 87395-63-9; **17**, 87395-64-0; **18**, 87395-65-1; **19**, 87395-66-2; benzophenone, 119-61-9; (+)-2α-tropanyl acetate, 64530-37-6; (+)-2α-tropanol, 36127-54-5; (+)-2α-tropanol hydrochloride, 87421-61-2; (+)-3-quinuclidinol hydrochloride, 25333-43-1.

(17) Toomey, R. F.; Riegel, E. R. *J. Org. Chem.* **1952**, *17*, 1492.

14β-(2-Bromoacetamido)morphine and 14β-(2-Bromoacetamido)morphinone

Sydney Archer,*,† Ahmad Seyed-Mozaffari,† Peter Osei-Gyimah,† Jean M. Bidlack,‡ and Leo G. Abood‡

Department of Chemistry, Cogswell Laboratory, Rensselaer Polytechnic Institute, Troy, New York 12181, and Center for Brain Research, The University of Rochester Medical Center, Rochester, New York 14642. *Received March 24, 1983*

14β-(2-Bromoacetamido)morphine (**6**) and 14β-(2-bromoacetamido)morphinone (**9**) were prepared preferably from the adduct of thebaine and 1-chloro-1-nitrosocyclohexane, which on reduction in methanol solution gave 14-aminocodeinone (**2**) and the corresponding ketal (**3**). When tested in a receptor-binding assay, the IC50 values of **6** and **9** were 15 and 10 nM, respectively. If the incubation time during the assay was increased from 15 to 30 min, irreversible binding of both ligands was observed.

Recently, we reported the partial purification of an opiate receptor from rat brain using an affinity column prepared from Aminohexylsepharose and 14β-(2-bromoacetamido)morphine (**6**).[1] The latter was prepared from 14β-nitrocodeinone,[2] but the yields were unsatisfactory. Because of the interest in the ligand, **6**, alternate synthetic approaches were investigated. In the course of this work, 14β-(2-bromoacetamido)morphinone (**9**) was prepared and tested in the receptor-binding assay for opiates[3] along with **6**. Both ligands were active, a prerequisite for use in affinity chromatography.

Chemistry. An improved procedure for the preparation of **6** and also for **9** is shown in Scheme I.

Thebaine (**1**) was treated with 1-chloro-1-nitrosocyclohexane and dry HCl to give an adduct, which was reduced with Zn and then partially hydrolyzed to a mixture of the ketone **2** and the ketal **3**.[4] Reduction of **2** with $NaBH_4$ gave **4**, which on demethylation gave **5**. Bromoacetylation, followed by treatment with 1 N HCl gave **6** in 30% overall yield from **2**.

The codeinone **2** was hydrogenated smoothly to **7**, but bromoacetylation gave a thermally unstable amide, which precluded further investigation in the dihydro series. On the other hand, bromoacetylation of either **2** or **3** proceeded uneventfully to afford **10** and **8**, respectively, both of which gave the morphinone **9** on treatment with BBr_3.

Biological Results

Rat neural membranes were prepared according to the method of Bidlack and Abood,[5] and the receptor binding assay was carried out according to Pert and Snyder.[3] [^{3}H]Dihydromorphine (80 Ci/mmol) at a concentration of 4 nM was used as the competing ligand. Under these conditions, the IC_{50} value of morphine was 4 nM. The ability of **6** and **9** to inhibit the binding of 4 nM [^{3}H]dihydromorphine to rat neural membranes was determined using seven different concentrations of each ligand in three different experiments. The IC_{50} value for each compound was determined from log-probit plots of the data. IC_{50} values of 15 and 10 nM were obtained for **6** and **9**, respectively.

† Rensselaer Polytechnic Institute.
‡ The University of Rochester Medical Center.

(1) Bidlack, J. M.; Abood, L.; Osei-Gyimah, P.; Archer, S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 636.
(2) Osei-Gyimah, P.; Archer, S. *J. Med. Chem.* **1980**, *23*, 162.
(3) Pert, C. B.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 2283.
(4) Horsewood, P.; Kirby, G. W. *J. Chem. Res., Miniprint* **1980**, 401; *J. Chem. Res., Synop.* **1980**, 4880.
(5) Bidlack, J. M.; Abood, L. *Life Sci.* **1980**, *27*, 331.

0022-2623/83/1826-1775$01.50/0