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(2-*exo*-3-*endo*)-2-Aryltropane-3-carboxylic Esters, a New Class of Narcotic Antagonists

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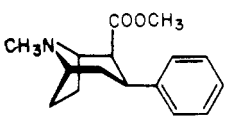
Tropanes **4** bearing an exo aromatic group on carbon-2, an *endo*-carbomethoxy group on carbon-3, and either a methyl group or a hydrogen on the nitrogen were found to be narcotic antagonists which were devoid of demonstrable analgesic activity. The activity resided in the 1*S* enantiomer. Compound **4** (R = *m*-hydroxyphenyl) showed an AD_{50} of 0.37 mg/kg sc and 1.8 mg/kg po (rats) as an antagonist in the Harris–Pierson modification of the D'Amour–Smith test. The tropane esters for this study were prepared by a Grignard reaction which gave essentially complete 1,4-addition in the absence of copper salts. Nearly equal quantities of esters epimeric at carbon-3 were formed.

In an earlier paper[1] we described some 3-*exo*-phenyltropane-2-*exo*-carboxylic esters (exemplified by **1** with



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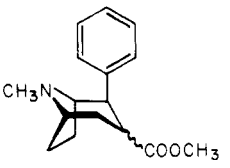


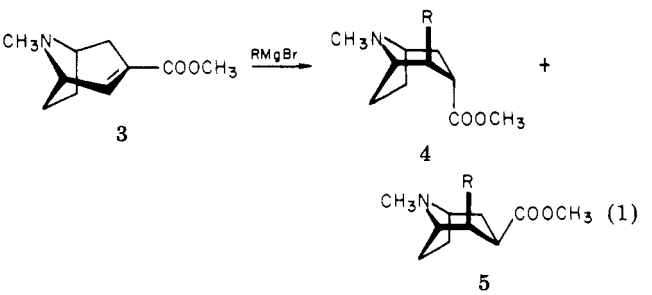
2

absolute configuration as drawn) which are powerful, orally active, central nervous system stimulants. Extremely restrictive configurational requirements for this activity were evident in this rigid molecule since activity was lost when the ester group was moved into an endo configuration or moved to the 4-exo position (the enantiomer of **1**) or when the ethylene bridge was removed.

We now report on a series of tropane esters, **2** (Table I), wherein the aromatic ring occupies the 2-exo position and the ester is in the 3 position. Those members which contain a 3-endo ester function are narcotic antagonists without accompanying analgesic activity, whereas their 3-exo counterparts are completely devoid of this activity. The present paper details this narcotic antagonism (Table II). Some hypoglycemic and analgesic activity associated with the 3-exo esters of this series is described separately in an accompanying paper.[2]

There is difficulty inherent in representing *R* and *S* enantiomers with a single general formula. The hypoglycemic esters referred to in the previous paragraph have the 1*R* configuration as drawn in **2**, whereas the active narcotic antagonists reported in the present paper have a 1*S* configuration (opposite that of **2**). Although most of the compounds in the present paper are racemates and either enantiomer could be used for general representation, the choice was made to show hereafter the representation of the enantiomers related to the narcotic antagonists. 1*S* configurations are drawn.

Chemistry. The desired esters were prepared by the reaction of Grignard reagents with unsaturated ester **3**[3] according to eq 1. As in the analogous series of esters **1**,[1]



3 **4** **5**

the presence of copper salts was not necessary in order to obtain 1,4-addition to this conjugated system. Further reaction of the primary products with RMgBr was minimized by adopting a reaction temperature of −20 to −25 °C and using ether rather than tetrahydrofuran as the solvent. Esters **4** and **5** were formed in nearly equal amounts.

Equilibration of this mixture with $NaOCH_3$ in CH_3OH shifted the ratio to about 1:15 of **4**–**5**, thus establishing the relationship of the two products as epimers and allowing configurational assignment. In the present series the conversion of endo ester **4** to exo ester **5** was a high-yield procedure in contrast to the esters of type **1** where β-elimination of the nitrogen could occur.[1]

Separation of esters **4** and **5** was accomplished by fractional crystallization and/or column and plate chromatography. Generally the 3-exo ester showed the larger R_f value in *i*-$PrNH_2$–Et_2O–pentane mixtures. However, the mixture of thienyl esters **36** was not resolvable by TLC. The 3-exo esters were readily recognizable by NMR since the aromatic ring was close enough to the ester function to shift the OCH_3 signal upfield by about 0.3 ppm from the OCH_3 signal positions seen in the 3-endo ester series. These peak positions are recorded in Table I.[4] Shift studies on these epimers using $Eu(fod)_3$ furnished limited

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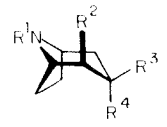
Table I. Tropane Esters



compd	R^1	R^2	R^3	R^4	formula	yield,[a] %	mp, °C	analyses	OCH_3, ppm[b]	$[\alpha]^{25}_D$, deg
(+)-9	CH_3	Ph	$COOCH_3$	H	$C_{16}H_{21}NO_2$	30.5	59-61[c,d]	C, H, N	3.31	
					$C_{16}H_{21}NO_2$·HCl		210-211[e-g]	C, H, Cl		
(−)-9	CH_3	Ph	$COOCH_3$	H	$C_{16}H_{21}NO_2$	38	90-91[f,h]	C, H, N		−16.3[i]
(+)-9	CH_3	Ph	$COOCH_3$	H	$C_{16}H_{21}NO_2$	25	90-91[f,h]	C, H, N		+16.6[i]
(±)-10	CH_3	Ph	H	$COOCH_3$	$C_{16}H_{21}NO_2$·HCl	28.5	227[j-l]	C, H, Cl	3.62	
(−)-10	CH_3	Ph	H	$COOCH_3$	$C_{16}H_{21}NO_2$·$C_6H_3N_3O_7$	24[r]	202-204[m,n,q]	C, H, N		−56.5[o]
					$C_{16}H_{21}NO_2$		121-123 (0.3 mm)[p,hh]	C, H, N		−38.7[i]
(+)-10	CH_3	Ph	H	$COOCH_3$	$C_{16}H_{21}NO_2$·$C_6H_3N_3O_7$	18[r]	201-203[m,n,q]	C, H, N		+55.6[o]
					$C_{16}H_{21}NO_2$	12	120-123 (0.3 mm)[p,ii]	C, H, N		+38.9[i]
11	$PhCH_2$	Ph	$COOCH_3$	H	$C_{22}H_{25}NO_2$	33	87-88.5[c,q]	C, H, N	3.30	
12	$PhCH_2$	Ph	H	$COOCH_3$	$C_{22}H_{25}NO_2$	43	oil		3.60	
13	H	Ph	$COOCH_3$	H	$C_{15}H_{19}NO_2$·HCl	83[r]	244-245[f,j,l]	C, H, Cl	3.40	
14	H	Ph	H	$COOCH_3$	$C_{15}H_{19}NO_2$·H_2SO_4·0.5H_2O	97	93.5-96.5[c,g]	C, H, S	3.66	
15	c-$C_3H_5CH_2$	Ph	H	$COOCH_3$	$C_{19}H_{25}NO_2$·HCl	61[r]	198-199[f,g,j]	C, H, Cl		
16	CH_3	Ph	COOH	H	$C_{15}H_{19}NO_2$·HCl·MeOH	94[r]	240-244[c,q,s]	C, H, Cl		
17	CH_3	Ph	H	COOH	$C_{15}H_{19}NO_2$·HCl	94[r]	258-259[c,e,q,t]	C, H, Cl		
18	CH_3	Ph	$COOCH(CH_3)_2$	H	$C_{18}H_{25}NO_2$·HCl	66	217-218[f,u]	C, H, Cl	*v*	
19	CH_3	Ph	H	$COOCH(CH_3)_2$	$C_{18}H_{25}NO_2$·HCl	74	249[j-l,t]	C, H, Cl	*w*	
20	CH_3	4-$PhCH_2O$-Ph	$COOCH_3$	H	$C_{23}H_{27}NO_3$	9	114-115[k,q]	C, H, N	3.33	
21	CH_3	4-$PhCH_2O$-Ph	H	$COOCH_3$	$C_{23}H_{27}NO_3$·$C_6H_3N_3O_7$[m,x]	29	179-180[y,z]	C, H, N	3.63	
22	CH_3	4-HO-Ph	$COOCH_3$	H	$C_{16}H_{21}NO_3$	81	212-213[c,aa]	C, H, N	3.32[bb]	
23	CH_3	4-HO-Ph	H	$COOCH_3$	$C_{16}H_{21}NO_3$	86	205-208[c,aa]		3.63[bb]	
					$C_{16}H_{21}NO_3$·HCl		218[c,j,aa]	C, H, Cl		
24	CH_3	3-$PhCH_2O$-Ph	$COOCH_3$	H	$C_{23}H_{27}NO_3$	19	93-94.5[f,q]	C, H, N	3.32	
25	CH_3	3-$PhCH_2O$-Ph	H	$COOCH_3$	$C_{23}H_{27}NO_3$·HCl	14	209[j-l]	C, H, Cl	3.60	
26	CH_3	3-HO-Ph	$COOCH_3$	H	$C_{16}H_{21}NO_3$·HCl	88[r]	238[c,e,aa]	C, H, Cl		
27	CH_3	3-HO-Ph	H	$COOCH_3$	$C_{16}H_{21}NO_3$·HCl	91[r]	192-193[c,e,l]	C, H, Cl		
28	$PhCH_2$	3-$PhCH_2O$-Ph	$COOCH_3$	H	$C_{29}H_{31}NO_3$	42	oil	C, H, N	3.25	
29	$PhCH_2$	3-$PhCH_2O$-Ph	H	$COOCH_3$	$C_{29}H_{31}NO_3$	42	oil	C, H, N	3.54	
30	H	3-HO-Ph	$COOCH_3$	H	$C_{15}H_{19}NO_3$·HCl	83[r]	234-236[j,cc,dd]	C, H, Cl		
(±)-31	H	3-HO-Ph	H	$COOCH_3$	$C_{15}H_{19}NO_3$·HCl	84[r]	220-222[e,aa]	C, H, Cl	3.63	
(−)-31	H	3-HO-Ph	H	$COOCH_3$	$C_{15}H_{19}NO_3$	88	222-223.5[k,aa]	C, H, N		−94.7[ee]
					$C_{15}H_{19}NO_3$·HCl·$\frac{1}{3}$EtOH		138.5-139.5[c,aa]	C, H, Cl		−64.4[ff]
(+)-31	H	3-HO-Ph	H	$COOCH_3$	$C_{15}H_{19}NO_3$	89	221-222.5[k,aa]	C, H, N		+93.4[ee]
					$C_{15}H_{19}NO_3$·HCl·$\frac{1}{3}$EtOH		138.5-139.5[c,aa]	C, H, Cl		+63.5[ff]
32	CH_3	3-CH_3O-Ph	$COOCH_3$	H	$C_{17}H_{23}NO_3$·HCl	11[r]	203-204[e,g,j]	C, H, Cl		
33	CH_3	3-CH_3O-Ph	H	$COOCH_3$	$C_{17}H_{23}NO_3$·HCl	16[r]	227-228[g,j,gg]	C, H, Cl	3.66	
34	CH_3	$PhCH_2$	$COOCH_3$	H	$C_{17}H_{23}NO_2$·HCl		218[e,g,k]	C, H, Cl	3.64	
35	CH_3	$PhCH_2$	H	$COOCH_3$	$C_{17}H_{23}NO_2$·HCl	54[r]	218[e,k,l]	C, H, Cl	3.66	
36	CH_3	2-thienyl	∿∿$COOCH_3$		mixture	$C_{14}H_{19}NO_2S$·HCl	77	168-169[e-g]	C, H, Cl	3.46, 3.72
37	CH_3	2-thienyl	$COOCH_3$	H	$C_{14}H_{19}NO_2S$·HCl	69	197-198[e,k,l]	C, H, Cl	3.46	
38	CH_3	1*H*-2-pyrrolyl	$COOCH_3$	H	$C_{14}H_{20}N_2O_2$	3	113-114[aa]	C, H, N	3.46	
39	CH_3	1*H*-2-pyrrolyl	H	$COOCH_3$	$C_{14}H_{20}N_2O_2$·HCl	17	232-234[c,e,aa]	C, H, Cl	3.71	

[a] The percent yields are of free base unless otherwise noted. [b] These NMR peaks were measured on the base in $CDCl_3$ unless otherwise noted. [c] Prisms. [d] From pentane. [e] Melts with intumescence. [f] Needles. [g] From acetone. [h] From MeOH with H_2O added. [i] 2% in $CHCl_3$. [j] Melts with decomposition. [k] Plates. [l] From CH_3CN. [m] Picrate salt. [n] Prisms and rods. [o] 2% in CH_3CN. [p] Boiling range. [q] From MeOH. [r] Yield of salt shown. [s] Softened progressively, 176–240 °C. [t] Melting point determined in an evacuated capillary. [u] CH_3CN with Et_2O added. [v] NMR showed nonequivalent CH_3 doublets at 1.22 and 1.61 ppm. [w] One CH_3 doublet at 1.72 ppm. [x] The free base is an oil. [y] From ethyl acetate. [z] Needles reverting to prisms. [aa] From EtOH. [bb] In DMF. [cc] From MeOH with Et_2O added. [dd] Partial melt at 167–177 °C, followed by resolidification. [ee] 1% in DMF. [ff] 1% in H_2O. [gg] Blades. [hh] n^{24}_D 1.5379. [ii] n^{24}_D 1.5378.

Table II. Prevention of Abdominal Constriction Response in Mice. Tail-Flick Narcotic-Antagonist Activity in Rats

compd	AcCh test, ED_{50}[a]		PPQ test, ED_{50}[a]		narcotic antag, AD_{50}[a,b]		observations[c]
	sc	po	sc	po	sc	po	
(±)-9	12 (7.8-17)		17 (14-20)		I		sed, 40 sc, M; sev trem, 120 sc, R
(±)-10	12 (9.6-14)	16 (9.5-27)	43 (34-56)	>200	5.5 (3.5-8.5)	1.1 (0.66-2.0)	sed, 40 sc, M; hypex, 100 sc, M; conv, 120 sc, R; neg bradykinin block, 100 sc, R
(−)-10					I		
(+)-10					3.3 (2.2-4.9)		
11	>75	21 (16-28)			I		
14	3.4 (2.5-8.2)	8.4 (4.3-13)	22 (16-29)	~100	2.1 (1.3-3.4)	4.1 (2.4-7.0)	dep, 75 sc, M; trem, 120 sc, R; neg bradykinin block, 50 sc
15	~10[d]				10 (6.4-15)		hypac, 30 sc, conv, 75 sc, M; 2/6 dead, 60 sc, R
17					I		
19	16 (14-19)				I		conv, 120 sc, R
23	7.1 (0.46-50)				I		hypac, 30 sc, M
26	24 (17-34)		~100[e]		I		0% block bradykinin response, 100 sc, R
27	16 (5.4-49)		~75		0.37 (0.25-0.54)	1.8 (1.1-3.0)	hypac, 75 sc, M; trem, hypac, 120 sc, R
(±)-31					2.0 (1.2-3.4)		
(−)-31	~60				I		
(+)-31	~60				~0.3[e]	14 (9.3-22)	
33	19 (14-26)				I		trem, dep, 35 sc and 5/15 dead, 50 sc, M
34	5.8 (2.3-19)				I		hypac, 75 sc, M; trem, 120 sc, R
35	4.4 (2.3-7.1)		20 (17-24)		54[f] (37-78)		conv, 100 sc, M; conv, 120 sc, R
36	13 (9.5-19)		~60		4.9 (3.1-7.8)		dep, 75 sc, M
37	12 (6.2-24)	35 (26-44)			I		conv, trem, rigid, 120 sc, R; act. agonist[i]
38	13 (9-19)	42 (30-58)			56 (35-90)		bradykinin test: 1/5 protected at 100 sc; 0/5 protected at 10 sc
39	18 (13-24)	34 (25-45)			I		bradykinin ED_{50} 8.5 (0.63-43) po; hypac, 200 po, R
40-41	16 (10-22)				I[g]		sev dep, 75 sc, M; conv, 3/6 dead, 120 ip, R
42					49[h] (29-83)		
43					5.6[h] (3.5-9.0)		
44	100% at 75, 0% at 25				1.45 (0.94-2.2)		dep, 75 sc, M
45					~2[i]		
A[j]	2.8 (1.5-7.7)		15 (10-23)		0.10 (0.07-0.14)	6.0 (4.4-8.2)	
B[k]	60 (50-76)		103 (83-128)		0.008 (0.006-0.012)		

[a] Dose in mg/kg, calculated as free base. [b] Antagonism vs. phenazocine. Compounds with an AD_{50} > 80 mg/kg are recorded as inactive (I). [c] Dose numbers refer to mg/kg; sed = sedation; trem = tremors; hypex = hyperexcitable; dep = depression; conv = convulsions; hypac = hyperactive; sev = severe; M = mice; R = rats. [d] 67% response at 15 mg; side effects at higher doses. [e] A flat dose-response curve led to this approximation. [f] Peak antagonism = 69% at 80 mg; lethal at 160 mg. [g] Inactive at 10 mg ip; side effects at higher doses. [h] Inactive vs. morphine and meperidine. [i] See Biological Studies. [j] Nalorphine. [k] Naloxone.

but consistent information. The most dramatic shift was one of 0.65 ppm by the C-4 axial H of epimer **5** (R = Ph) upon addition of 0.1 mol of shift reagent per mole of **5**. ^{13}C NMR peak positions for **4** and **5** (R = Ph) are reported in Table III.

The exo configuration of the aromatic ring on C-2 with attendant crowding in the vicinity of the nitrogen was substantiated by failure of either Grignard product (**4** or **5**, R = Ph) to react significantly with ethyl iodide in refluxing ether (28 h).[1,5] Compounds **4** and **5** (R = Ph) showed $J_{H_2H_3}$ = 4.5 and 6.5 Hz, respectively (5% in $CDCl_3$), which are consistent with a considerably flattened chair form for the piperidine moiety. Were the aromatic ring in a truly axial conformation, the J values would have been close to 3.5 Hz.

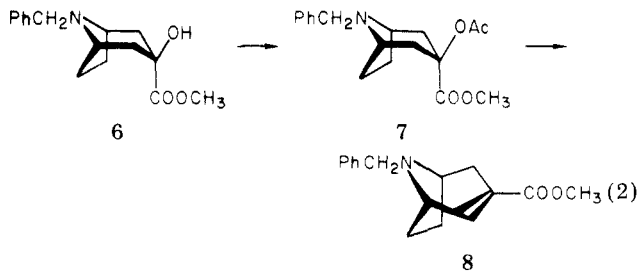
When compound **4** (R = Ph) proved to have considerable activity as a narcotic antagonist, a structure–activity study was initiated. Table I lists the esters prepared for this purpose with **4** and **5** (R = Ph) appearing as compounds **10** and **9**, respectively. The specific reaction of unsaturated ester **3** with PhMgBr to form **9** and **10** constitutes a prototype reaction which will be referred to in the Experimental Section as the "standard method".

The enantiomers of **9** and **10** were prepared by reaction of PhMgBr with the enantiomers of unsaturated ester **3**, the absolute configurations of which have been established.[6] (1*R*)-**3** (dextrorotatory) furnished levorotatory **10** so the latter has the cocaine (1*R*) configuration as does its coproduct (−)-**9**. It is the 1*S* enantiomer, (+)-**10**, which is a narcotic antagonist. Resolution of the *m*-hydroxy analogue of **10** (compound **31**) by means of (−)-diisopropylidene-2-keto-L-gulonic acid monohydrate[7] furnished pure enantiomers, only one of which [(+)-**31**] was a narcotic antagonist. Assignment of (+)-**31** as 1*S* was made on this basis.

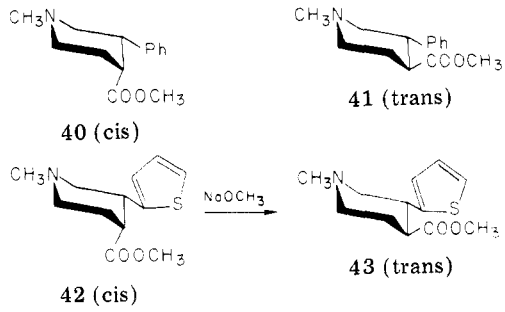
The method for separating the exo and endo epimers (−)-**9** and (−)-**10** produced in the reaction of (+)-**3** with PhMgBr as just mentioned took advantage of special solubility characteristics. It was possible to precipitate about 50% of the (−)-**9** present directly from the mixture by dissolving the latter in MeOH and adding H_2O. The remaining mixture was dissolved in EtOH and treated with 1 equiv of levorotatory dibenzoyltartaric acid in EtOH. The salt of (−)-**9** so produced was considerably less soluble than the corresponding salt of (−)-**10**, thereby separating another 40% of (−)-**9**. The axial epimer (−)-**10** was then separated as its picrate salt from which the free base was isolated and distilled. This same method was used to separate (+)-**9** (3-exo) from (+)-**10** (3-endo). GLC demonstrated that the epimers were pure. It proved possible to effect complete purification of these epimers on certain batches of silica gel preparative plates using multiple passes of 2:20:78 isopropylamine–ether–pentane, but the process could not be reproduced in the latter stages of the work owing to presumed changes in the silica gel available.

Production of an 8-nortropane-3-carboxylic ester, needed as an intermediate for a variety of N-substituted derivatives, presented some difficulty. Since the presence of a large exo substituent on C-2 inhibited quaternary ammonium ion formation[1,5] which was required for removal of the *N*-methyl group by usual means (ROCOCl, CNBr), an *N*-benzyl precursor was made which could be catalytically debenzylated. Thus, unsaturated ester **8** was prepared according to eq 2 and treated with RMgBr to furnish those compounds of Table I wherein R^1 = $PhCH_2$. Debenzylation and N-alkylation were uneventful.

Only one pair of compounds was made (**34** and **35**) wherein the aromatic ring was separated from the tropane skeleton by a methylene group.



Some unbridged piperidines (**40**–**43**) were studied in order to determine the role of ring rigidity in the biological activity of the present series. The known isomers, **40** and **41**, of methyl 1-methyl-3-phenylpiperidine-4-carboxylate[8] probably exist very largely in the conformations shown and with an extremely low population of the trans conformation such as found in tropane **4** (R = Ph). These isomers were tested as a mixture. The corresponding unbridged thienyl esters **42** and **43**, however, were separated and their structures assigned on the basis that **42** was transformed almost entirely to **43** upon treatment with $NaOCH_3$ in CH_3OH.



Biological Studies. The biological activity of the compounds presently reported was evaluated by means of four test procedures. Activity in preventing the abdominal constriction response (also referred to as antiwrithing activity) in mice was measured using the procedure of Collier et al.,[9] wherein acetylcholine (AcCh) was the inducing agent, and that of Pearl and Harris,[10] wherein phenyl-*p*-benzoquinone (PPQ) was the inducing agent. Narcotic analgesia was determined in rats by a modified D'Amour–Smith "tail-flick" method[11] described by Harris and Pierson. Narcotic antagonism was evaluated according to a procedure of these same investigators.[12] In a more definitive test for analgesia than prevention of the abdominal constriction response, five compounds were examined for their ability to block the intraarterial bradykinin-evoked response in rats.[12] Table II summarizes the test results. Confidence limits for the AcCh and PPQ data were calculated by the method of Bliss;[13] limits for the tail-flick data were calculated by the method of Litchfield and Wilcoxon.[14]

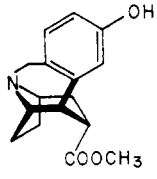
(±)-**10** antagonized phenazocine with an AD_{50} of 5.5 mg/kg sc and appeared to be somewhat more effective orally (AD_{50} = 1.1 mg/kg). It was also an effective antagonist of morphine (AD_{50} = 29 mg/kg sc and 13 mg/kg po) and meperidine (AD_{50} = 19 mg/kg sc and 25 mg/kg po). This compound had no agonist activity in the rat tail-flick test at 120 mg/kg sc and showed only moderate activity in preventing the abdominal constriction response. Finally, it demonstrated no analgesia at doses up to 100 mg/kg sc as determined in the bradykinin test.

The dextrorotatory (1*S*) enantiomer of **10** was the source of the observed antagonist action. The 1*R* enantiomer was inactive. Likewise, with the pair of *m*-hydroxy analogues

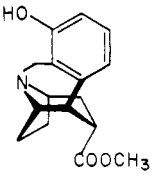
(31), only one enantiomer was active. Attempts to superimpose models of (+)-10 or (+)-31 upon those of allylnormorphine or naloxone showed no similarity. This is not surprising, since such groups as allyl or cyclopropylmethyl must replace the normal *N*-methyl group of the morphine series in order to develop the antagonist action. In the present series, the *N*-methyl compounds are antagonists and introduction of a cyclopropylmethyl group (15) tends to lower the potency.

The observation that (±)-10 was slightly more active orally than subcutaneously as a narcotic antagonist raised the question of metabolite involvement. A likely metabolite, the demethyl homologue 14, showed no real difference in activity by the two routes and was of the same order of activity. Hydroxylation of the aromatic ring was another metabolic possibility. The *p*-hydroxy analogue 23 had no antagonist activity, but the *m*-hydroxy analogues 27 and (+)-31 were the most active members of the series. The methyl ether (33) of 27 was inactive. As was the case with compound (±)-10, neither 14 nor 27 showed any agonist activity in the tail-flick test at 120 mg/kg sc.

Since moving a hydroxyl group on the benzene ring from the meta (27) to the para position (23) caused loss of antagonist activity, it was surmised that the position in space of this hydroxyl was quite critical. Compounds 44 and 45 became available in the course of some deme-



44



45

thylation studies on tropanes.[15] In view of the considerable difference in location of the hydroxyl groups here, there was surprisingly little difference in the narcotic antagonist AD_{50} values between these compounds. 44 showed 1.45 (0.94–2.2) mg/kg sc, whereas the value for 45 lay between 1 and 10 and was probably close to 2 mg/kg sc. The small amount of 45 available led to the uncertainty in the latter case.

Any appreciable modification at tropane carbon-3 destroyed this antagonist action. For example, the 3-*endo*-carboxylic acid 17 and the isopropyl ester 19 were both inactive. All 3-exo epimers tested (9, 11, 26, 34, 37, and 38) were inactive as antagonists except 38 which showed weak action as noted below.

Replacement of the phenyl ring on C-2 by 2-thienyl (36) seems to have maintained activity even though the product contained about 50% of the 3-*exo*-carbomethoxy epimer which could not be separated. A 2-benzyl group (35) afforded only weak activity and the 2-(1*H*-2-pyrrolyl) analogue 39 was inactive. Surprisingly, the exo pyrrolyl epimer 38 showed very weak (56 mg/kg sc) antagonist action. On the basis of biological activity, one would be tempted to question the structural assignments of 38 and 39 but NMR and thermodynamic data supported those assignments given.

The inactivity of mixture 40–41 and the limited activities of 42 and 43 (inactive vs. morphine and meperidine) indicate that there are severe conformational restrictions for the narcotic antagonist activity in this series and that the ethylene bridge is necessary in order to maintain the required conformational integrity.

In summary, a group of narcotic antagonists is reported which does not fall into the well-known category of agonists/antagonists such as pentazocine, cyclazocine, and nalorphine, all of which are active in the bradykinin test for analgesia. For example, nalorphine has an ED_{50} of 5 mg/kg sc in this test.[12c] The compounds of the present series are inactive in the bradykinin test but do block AcCh-induced writhings as does the "pure antagonist" naloxone albeit at extremely high doses [ED_{50} = 60 (50–76) mg/kg sc, mice].

Although all analgesics are active in the antiwrithing tests, this activity is by no means specific. Many "false positives" have been reported among classes of compounds not considered to be analgesics, e.g., sympathomimetics, central nervous system stimulants, central nervous system depressants, anticholinergics, and antihistaminics.[9,10,16] The failure of representatives (10, 14, and 26) of the present series to demonstrate activity in the bradykinin test is a stong indication that their antiwrithing activity is due to some property other than analgesia and that there is no real evidence for any analgetic component in the activity observed.

Experimental Section

Analytical results for indicated elements are within ±0.4% of the theoretical values on all new compounds reported. Analysis of mixtures by GC was done isothermally at 230 °C using a 5 ft × 2 mm column of 10% Carbowax 20M on 100–120 mesh Gas-Chrom Q. The injection port was held at 245 °C and the flame ionization detector was at 250 °C. Where Grignard reactions were difficult to start, between 0.2 and 1 mL of $(CH_2Br)_2$, together with a corresponding amount of Mg, was added as the activator. Preparative plate chromatography was done with Brinkmann PF_{254} silica gel in 1–1.5-mm thickness on 20 × 40 cm glass plates. Melting points were measured in capillary tubes and are uncorrected.

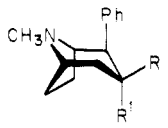
NMR spectra were recorded on a Varian HA-100 spectrometer using Me_4Si as an internal standard. All new compounds reported gave NMR spectra compatible with their structures. IR spectral studies on hydrogen bonding were done using a Beckmann IR-7 spectrophotometer.

Preparation of Methyl (1*RS*)-8-Methyl-8-azabicyclo-[3.2.1]oct-2-ene-3-carboxylate (3). This unsaturated ester was prepared by the method of Zirkle et al.[3] with the following modification. Instead of passing methyl (3-*endo*)-3-acetoxy-8-methyl-8-azabicyclo[3.2.1]octane-3-carboxylate through a hot tube containing glass beads, this ester (154 g, 0.64 mol) was added, with stirring, in 3 min to 1.5 L of Nujol at 330 °C in a 3-L, three-necked, round-bottomed flask fitted with a dropping funnel, stirrer, short distillation head, and condenser. The mixture was heated at 315–325 °C for 5 min and then cooled as rapidly as possible with an electric fan. Considerable product and HOAc were distilled during the process. The combined reaction mixture and distillate were poured into 2 L of hexane, and the product was extracted with 350 and 250 mL of 2 N aqueous HCl. Saturation (with cooling) of the aqueous extracts with K_2CO_3, extraction with Et_2O, and distillation afforded 71.7 g (62%) of 3, bp 60–65 °C (0.1 mm). Yields ranged from 60 to 75% on various runs.

Standard Method. Reaction of Methyl (1*RS*)-8-Methyl-8-azabicyclo[3.2.1]oct-2-ene-3-carboxylate (3) with Phenylmagnesium Bromide. A solution of 48.5 g (0.268 mol) of 3 in 200 mL of Et_2O was added dropwise, with stirring, in 40 min to 135 mL (0.40 mol) of 3 M PhMgBr (in Et_2O) in 350 mL of Et_2O, the internal temperature being held at −23 ± 2 °C. The mixture was stirred at this temperature for 1 h and then poured into 500 mL of 2 N HCl and 250 g of ice with vigorous stirring.

The layers were separated, and the water layer was washed with Et_2O and made strongly alkaline with concentrated NH_4OH. Extraction with Et_2O gave 68 g of oily product which was distilled. The products of interest (55.6 g) were collected at 116–130 °C (0.25–0.35 mm). GC showed a 52:48 ratio (3-exo–3-endo) of the major components. Dilution of this distillate with 50 mL of pentane and chilling gave 10.2 g of massive prisms of **methyl (1*RS*-*exo*,*exo*)-8-methyl-2-phenyl-8-azabicyclo[3.2.1]nonane-3-carboxylate [(±)-9].** It was recrystallized twice by melting, diluting with 2 vol of pentane, cooling, and seeding to give compound (±)-9 of Table I (see also Table III).

Table III. ^{13}C Chemical Shifts[a,b]



carbon no.	9, R = $COOCH_3$; R^1 = H	10, R = H; R^1 = $COOCH_3$
C-1	67.5	66.5
C-2	37.5	40.2
C-3	49.3	48.9
C-4	32.2	32.9
C-5	60.7	59.5
C-6 }	26.6	26.4
C-7 }	24.8	25.3
ipso	142.2	146.0
other Ar-C	129.4	129.3
	128.4	127.8
	127.3	127.4
	125.9	125.7
C=O	174.1	176.0
OCH_3	50.8	51.4
NCH_3	41.7	40.4

[a] The δ values are in parts per million downfield from Me_4Si; δ (Me_4Si) = δ ($CDCl_3$) + 76.9 ppm. [b] For other ^{13}C spectral data on tropanes, see M. Lounasmaa, P. M. Wovkulich, and E. Wenkert, *J. Org. Chem.*, 40, 3694 (1975).

A 6-g portion of the oily residue remaining after separation of the 10.2 g of prisms above was chromatographed on 27 preparative silica gel plates using multiple passes of a 1.5:20:78.5 *i*-$PrNH_2$–Et_2O–pentane solvent system. The less polar of the two major bands furnished 1.56 g of ester (±)-**9** described above. The more polar band yielded 2.93 g of oily **methyl (1*RS*-2-*exo*-3-*endo*)-8-methyl-2-phenyl-8-azabicyclo[3.2.1]nonane-3-carboxylate.** Its hydrochloride salt is compound (±)-**10** of Table I (see Table III).

Epimerization of Methyl (1*RS*-2-*exo*-3-*endo*)-8-Methyl-2-phenyl-8-azabicyclo[3.2.1]nonane-3-carboxylate [(±)-10]. A solution of 10.0 g (0.39 mol) of the crude 52:48 mixture (by GC) of (±)-**9** and (±)-**10** produced directly from the Grignard reaction described above and 0.5 g (0.009 mol) of $NaOCH_3$ in 50 mL of MeOH was refluxed for 3 h and concentrated by warming in vacuo. Et_2O and brine were added, and the Et_2O layer was washed with brine. Concentration of the Et_2O layer gave an oil which, by GC analysis, consisted of 6% (±)-**10** (retention time 17.2 min) and 94% (±)-**9** (retention time 18.8 min). Treatment of the crude product with ethereal HCl and dual recrystallization of this salt from acetone gave 5.1 g of pure exo ester hydrochloride (±)-**9**, mp 210–211.5 °C.

Reaction of the 1*R* Enantiomer of 3 with PhMgBr. A solution of 11.18 g (0.0619 mol) of the 1*R* (dextrorotatory) enantiomer of unsaturated ester **3**[6] in Et_2O was added to phenylmagnesium bromide in the manner just described for (1*RS*)-**3**. Distillation of the crude product gave 14.78 g (92%) of material which distilled at 115–121 °C (0.2 mm), its being a mixture epimeric at C-3. This distillate was dissolved in 50 mL of hot MeOH, and 18 mL of H_2O was added. Cooling to 20 °C caused separation of needle clusters. Cooling at 0 °C and filtration (washed with 10 mL of the same solvent mixture) gave 4.39 g of **methyl (1*R*-*exo*,*exo*)-8-methyl-2-phenyl-8-azabicyclo-[3.2.1]octane-3-carboxylate [(−)-9].**

The filtrate from collection of (−)-**9** was concentrated in vacuo to remove MeOH, and the oily esters (11.0 g, 0.0424 mol) were extracted with Et_2O. A solution of this oil in 20 mL of absolute EtOH was added to a solution of 15.96 g (0.0424 mol) of levorotatory (natural) dibenzoyltartaric acid monohydrate in 30 mL of absolute EtOH. After 4 h at 25 °C the precipitate of needles was collected and air-dried. The resulting 7.24 g of the salt of base (−)-**9** was treated with 10 mL of 2 N HCl, and the liberated dibenzoyltartaric acid was washed away with Et_2O. Addition of concentrated NH_4OH to the aqueous solution, followed by extraction with Et_2O, afforded 2.89 g more of (−)-**9**. The 7.28-g total of (−)-**9** thus separated was dissolved in 24 mL of boiling MeOH, 8 mL of warm H_2O was added, and the solution was cooled to give 6.07 g of pure (−)-**9** (Table I). Dilution of the filtrate with more water (7 mL) almost produced permanent cloudiness but very little further (−)-**9** separated.

The ethanolic filtrate from separation of 7.24 g of the dibenzoyltartrate salt of (−)-**9** was concentrated by warming in vacuo (<60 °C), the residue was treated with 20 mL of 2 N HCl, and the liberated acid was removed with ether. Addition of concentrated NH_4OH to the aqueous layer and extraction with Et_2O afforded 6.9 g of predominantly **methyl (1*R*-2-*exo*-3-*endo*)-8-methyl-2-phenyl-8-azabicyclo[3.2.1]octane-3-carboxylate [(−)-10].** GC analysis indicated 10% of (−)-**9** was still present.

An ethereal solution of 6.9 g of (−)-**10** was treated with ethereal HCl, and the collected salt was dissolved in 25 mL of warm CH_3CN. Cooling caused separation of small, nearly square plates (0.98 g). Dilution of the mother liquor with an equal volume of Et_2O caused separation of only 0.13 g of more plates. Recrystallization of this 1.11 g of salt from 15 mL of MeOH boiled down to a 6-mL volume gave 0.93 g of *dl* salt (±)-**10**: mp 225 °C dec; $[\alpha]^{25}_D$ 0° (2% in H_2O). The 1.11 g of salt represents 0.97 g of free base or 6% of theory.

The mother liquor from separation of 1.11 g of HCl salt was concentrated to a residue by warming in vacuo, the residue was made basic with NH_4OH, and the liberated base was separated with Et_2O. Distillation of the resulting 5.55 g of oil gave 5.13 g (32%) of (−)-**10** which, at this point, probably contained about 12% of 3-exo ester (−)-**9**. This oil in 175 mL of Et_2O was treated with 4.53 g of picric acid in CH_2Cl_2, and the precipitated salt was recrystallized from 350 mL of MeOH with concentration to 225 mL to give 7.24 g of yellow prisms and rods of mp 202–204 °C which was unchanged by further recrystallization (see (−)-**10**, Table I). Treatment of this salt with 60 mL of 0.5 N NaOH and extraction with Et_2O, concentration of the extract, and extraction with pentane separated the base which was distilled to give pure (−)-**10** (Table I). GC analysis showed that the residual 3-exo ester had been effectively removed.

Reaction of the 1*S* Enantiomer of 3 with PhMgBr. The efficient procedure described immediately above for the 1*R* enantiomer of **3** was actually worked out on the present 1*S* enantiomer, and thus the actual amounts of products finally isolated were reduced. From 10.57 g (0.0584 mol) of (levorotatory) (1*S*)-**3**[6] were obtained 3.75 g of **methyl (1*S*-*exo*,*exo*)-8-methyl-2-phenyl-8-azabicyclo[3.2.1]octane-3-carboxylate [(+)-9]** and 1.85 g of **methyl (1*S*-2-*exo*-3-*endo*)-8-methyl-2-phenyl-8-azabicyclo[3.2.1]octane-3-carboxylate [(+)-10].**

Attempted Quaternization of a 1:1 Mixture of (±)-9 and (±)-10. A 0.3-g sample of the oily, distilled mixture of (±)-**9** and (±)-**10**, obtained as described in their preparation, was dissolved in 3 mL of Et_2O and 0.3 mL of EtI, and the solution was refluxed for 28 h. Only 10 mg of ether-insoluble material separated and TLC showed that the solution contained only starting material.

Compounds **11** and **12** were prepared by the standard method from methyl (1*RS*)-8-benzyl-8-azabicyclo[3.2.1]oct-2-ene-3-carboxylate (**8**) which was synthesized in the following manner. Methyl (3-*endo*)-8-benzyl-3-hydroxy-8-azabicyclo[3.2.1]octane-3-carboxylate (**6**)[17] (42.0 g, 0.153 mol) was refluxed with 175 mL of acetic anhydride, the mixture was concentrated at up to 90 °C (10 mm), and the residual oil was diluted with 100 mL of Et_2O. This solution was stirred with 100 mL of saturated aqueous $NaHCO_3$ for 1 h, 5 g of solid $NaHCO_3$ was added, stirring was continued for 1 h, and the ether layer was separated and dried. Concentration gave 46.9 g (97%) of methyl (3-*endo*)-3-acetoxy-8-benzyl-8-azabicyclo[3.2.1]octane-3-carboxylate (**7**) as a colorless oil: IR (oil film) 1748 and 1736 cm^{-1}; NMR δ 3.73 (s, 3 H, OCH_3) and 3.61 (s, 2 H, $NCH_2C_6H_5$). Anal. ($C_{18}H_{23}NO_4$) C, H, N.

Pyrolysis of ester **7** was accomplished by adding a vigorously swirled, nonhomogeneous mixture of 46.8 g (0.148 mol) of **7** and 50 mL of Nujol mineral oil at 100 °C in about 1 min to 450 mL of stirred Nujol at 325 °C. There was no frothing. A stream of N_2 was blown onto the surface to remove liberated acetic acid. The internal temperature dropped to 310 °C but was back to 325 °C within 2 min under external heating. After 4 min of reaction time the mixture was poured into a large beaker to achieve rapid cooling. This mixture was diluted with 1 L of Et_2O and extracted with 200 and 100 mL of 2 N HCl. The acid extracts were made

alkaline with 35% NaOH, and the liberated base was extracted with Et_2O and distilled: bp 144–149 °C (0.65 mm); 27.9 g (73%); n^{25}_D 1.5542; IR (oil film) 1715 cm^{-1}; UV λ_{max}^{EtOH} 257.5 nm (ϵ 750) and 266.5 (450) plus end absorption; NMR compatible for unsaturated ester **8**. Anal. ($C_{16}H_{19}NO_2$) C, H, N.

Compounds **11** and **12** were then prepared from this unsaturated ester **8** and PhMgBr. GC on the crude, distilled product [bp 190–209 °C (0.7 mm)] showed a 1:1 mixture of epimers **11** and **12**. Partial separation was accomplished through formation of picrate salts. The picrate of **12** crystallized from the EtOAc solution upon addition of Et_2O. The picrate of **11** failed to crystallize. The mixture of bases from the filtrate was then separated by silica gel chromatography.

Compounds **13** and **14** were prepared from **11** and **12** by catalytic hydrogenation in EtOH in the presence of 1 equiv of 2 N aqueous HCl using 1 g of 10% Pd/C per 6 g of amine with hydrogen under 60 psig.

Compound **15**. To a mixture of 7.18 g (0.029 mol) of **14**, 8.4 g (0.1 mol) of solid $NaHCO_3$, and 50 mL of DMF was added 8.1 g (0.06 mol) of cyclopropylmethyl bromide. The mixture was stirred on the steam bath for 1 h, stripped of solvent by warming in vacuo, and extracted with Et_2O. HCl was bubbled into the Et_2O solution and the precipitated gummy salt was triturated with 2 × 25 mL of EtOAc and 3 × 10 mL of acetone to give 6.55 g of powdery **15**·HCl. It was then recrystallized to give compound **15** of Table I.

Compounds **16** and **17** were prepared from (±)-**9** and (±)-**10** by hydrolysis using refluxing 2 N HCl (7 equiv, 21 h). Removal of solvent and trituration with acetone gave the crystalline HCl salt of **16**. **17** crystallized spontaneously upon solvent removal.

Compounds **18** and **19** were prepared from a 1:1 mixture of acids **16** and **17** by treating a solution of 12.5 g (0.044 mol) of the mixture in 150 mL of isopropyl alcohol with gaseous HCl at reflux for 5 h. Concentration of the solution, treatment with excess 2 N NaOH, and extraction with ether gave a mixture of esters (13.3 g, 92%) which was converted to HCl salts with Et_2O·HCl. When the powdery salt mixture was dissolved in 50 mL of warm CH_3CN, plates precipitated spontaneously. Cooling below 25 °C caused coprecipitation of needles so filtration was done at 25 °C to give 4.6 g of pure plates of endo ester **19**. Concentration to a 20-mL volume and cooling to 25 °C gave a second crop of 0.67 g (total of 5.27 g or 74% yield based on the amount of endo acid present in the starting material). Dilution of the 20-mL mother liquor with 25 mL of Et_2O precipitated 4.7 g (66%) of exo ester **18**.

Compounds **20** and **21** were prepared by the standard method from 18.1 g (0.10 mol) of unsaturated ester **3** and RMgBr made from 12.0 g (0.5 g-atom) of magnesium, 79.0 g (0.30 mol) of benzyl 4-bromophenyl ether, and 200 mL of THF. The ester **3** was dissolved in 100 mL of THF for addition. Distillation of the crude reaction product at 0.15-mm pressure gave 9.1 g of a mixture of **20** and **21**, bp 220–238 °C. There was a 16-g still-pot residue. The mixture of **20** and **21** (1:3 ratio) was separated on 31 20 × 40 cm silica preparative plates using 3:40:57 *i*-$PrNH_2$–pentane–Et_2O.

Compounds **22** and **23** were prepared by catalytic debenzylation of **20** and **21** in EtOH using 10% Pd/C under 60 psig of hydrogen pressure. No HCl was present. The bases crystallized upon concentration of the reaction solvent.

Compounds **24** and **25** were prepared by the standard method using 18.1 g (0.10 mol) of ester **3** and a Grignard reagent prepared from 39.5 g (0.15 mol) of benzyl 3-bromophenyl ether, 4.9 g (0.20 g-atom) of magnesium, and 200 mL of Et_2O. The Grignard reagent and solvent formed two layers. The crude product was distilled rapidly [180–215 °C (0.6 mm)], giving 17.2 g of an oily epimeric mixture. Treatment of this oil in Et_2O with excess Et_2O·HCl and trituration of the precipitated salt with acetone gave 5.8 g of essentially pure axial epimer **25**·HCl.

The mother liquor from separation of the axial epimer was shown by NMR to contain 85% of the equatorial epimer. The oily base from this liquor crystallized. It was recrystallized from MeOH to give 6.78 g of **24** base.

Compounds **26** and **27** were prepared from **24** and **25** by catalytic debenzylation in EtOH using 10% Pd/C under 60 psig of hydrogen pressure. Compound **25** was reduced in the form of its HCl salt. One equivalent of 2 N HCl was added to the reaction mixture containing **24**. Trituration with CH_3CN and with acetone caused the salts of **26** and **27** to crystallize.

Compounds **28** and **29** were prepared by the standard method using 29.0 g (0.113 mol) of *N*-benzyl ester **8** and a Grignard reagent prepared from 63.5 g (0.24 mol) of benzyl 3-bromophenyl ether, 8.9 g (0.37 g-atom) of magnesium, and 600 mL of Et_2O. The Grignard reagent mixture formed two layers. After the quench process, addition of 2 N HCl caused precipitation of the product hydrochloride of low water solubility. The base was recovered by treatment with NH_4OH and Et_2O extraction. The crude, oily product, 49.9 g (100%), was chromatographed on 2 kg of activity grade II–III Woelm basic alumina with rechromatography of the transitional fractions. The exo epimer **28** was eluted *after* the endo epimer **29**.

Compounds **30** and (±)-**31** were prepared from **28** and **29** by catalytic debenzylation in EtOH containing 1 equiv of 2 N HCl using 10% Pd/C and 60 psig of hydrogen pressure.

Resolution of (±)-31. To a solution of 6.37 g (0.0218 mol) of (–)-diisopropylidene-2-ketogulonic acid monohydrate[7] in 23 mL of absolute EtOH at 40 °C was added 5.69 g (0.0218 mol) of basic ester (±)-**31**. The latter dissolved and there was almost immediate precipitation of the (+)-base (–)-gulonate salt. The solution was chilled, and the precipitate was collected and washed with three 1-mL portions of cold EtOH: 6.20 g, 103% of theory for a single diastereoisomer. This salt was treated with 50 mL of H_2O and 15 mL of concentrated NH_4OH, and the crystalline (+)-**31** was collected: 2.71 g, 95% from (±)-**31**. One recrystallization from EtOH gave 2.54 g of analytically and optically pure (+)-**31** which was assigned the 1*S* configuration on the basis of analogy in biological activity with 1*S* compound (+)-**10**.

The alcoholic filtrate and washings from separation of the (+)-base salt above were concentrated to a residue by warming in vacuo, and the residue was treated with 25 mL of H_2O and 15 mL of concentrated NH_4OH to give 2.79 g (98%) of crystalline (–)-**31** (1*R* configuration). One recrystallization from EtOH gave 2.52 g of analytically and optically pure base.

Compounds **32** and **33** were made according to the standard method using 10 g (0.055 mol) of ester **3** and a Grignard reagent prepared from 25.8 g (0.14 mol) of *m*-bromoanisole and 4.0 g (0.16 g-atom) of magnesium in 120 mL of Et_2O. The Grignard reagent partially precipitated as an oily layer. Distillation of the crude reaction product gave 7.0 g (50%) of a mixture of **32** and **33**, bp 143–147 °C (0.35 mm). A small quantity of the mixture of epimers was spread on silica preparative chromatoplates which were developed with 1:49:50 *i*-$PrNH_2$–EtOAc–pentane. The less polar epimer (*endo*-$COOCH_3$) from the plates formed a crystalline HCl salt. The remainder of the epimeric mixture was treated with Et_2O·HCl, and the precipitated gum was triturated with acetone while seeding with the crystalline salt isolated above. Endo ester **33**·HCl (2.9 g) was collected and purified by one recrystallization from acetone. Concentration of the filtrate to a small volume and cooling gave 1.9 g of exo ester **32**·HCl. One recrystallization purified it.

Compounds **34** and **35** were prepared by reaction of benzylmagnesium bromide (0.14 mol) with ester **3** (0.07 mol) using the standard method. The crude basic product (99%) was converted to a pasty salt with ethereal HCl. Trituration with 40 mL of acetone and washing with 3 × 15 mL of this solvent afforded 17.7 g of crisp solid. Recrystallization from CH_3CN gave 11.7 g of axial compound **35**·HCl. The free base was an oil.

The mother liquor residue (4.63 g) from recrystallization of the axial ester **35** was a mixture of **34** and **35**. It was converted to **34** by refluxing it with 2.0 g of $NaOCH_3$ in 40 mL of MeOH for 2 h, removing the solvent, adding H_2O, and extracting the product with Et_2O. The oily base (3.06 g) crystallized. It was melted, diluted with an equal volume of pentane, and allowed to crystallize to give pure **34**.

Epimeric Mixture 36 and Exo Ester 37. A mixture of C-3 epimers was prepared by the standard method from 18.1 g (0.10 mol) of unsaturated ester **3** and a Grignard reagent made from 24.5 g (0.15 mol) of 2-bromothiophene and 4.8 g (0.2 g-atom) of magnesium using Et_2O as solvent. Distillation of the crude basic product gave 20.47 g (77%) of a 1:1 epimer mixture, bp 111–122 °C (0.2 mm). The HCl salt, formed with Et_2O·HCl, was triturated with acetone and then recrystallized from 35 mL of CH_3CN with cooling only to 30 °C. Needle tufts separated (5.1 g) which were recrystallized from CH_3CN to give the HCl salt of exo ester **37** which then precipitated as plates.

Concentration of the mother liquor from separation of **37**·HCl gave 5.9 g of a mixture of needles and plates. Recrystallization of this solid from acetone afforded 5.0 g of a 45:55 mixture of hydrochlorides of the exo and endo esters, respectively, which was characterized and tested under the designation of compound **36**. The pure endo (axial) ester was not obtained by fractional crystallization or otherwise. TLC failed to separate these epimers.

Compound 37 by Epimerization. When a crude, distilled, epimeric mixture obtained as above (92.6 g) was dissolved in 400 mL of MeOH, treated with 2.0 g of $NaOCH_3$, and refluxed for 3.5 h under N_2, removal of the solvent and extraction of the basic ester with Et_2O gave 92 g of a sticky crystalline mixture which (by NMR) contained 95% of the exo (equatorial) ester and 5% of the endo (axial) epimer. It was placed in a funnel and 125 mL of 1:1 Et_2O–pentane was percolated through it, thereby leaving 74.9 g of essentially pure exo epimer **37**. Concentration of the percolate to a 25-mL volume and cooling gave 8.34 g more of the exo epimer (total of 83.3 g, 96%).

Compounds **38** and **39** were prepared by the standard method through reaction of 2-pyrrolylmagnesium bromide [prepared from 33.5 g (0.50 mol) of pyrrole and 168 mL (0.50 mol) of ethereal 3 M CH_3MgBr in 200 mL of Et_2O] with 30.0 g (0.167 mol) of **3** in 190 mL of Et_2O. Distillation of the crude product gave 19.4 g (47%) of oil: bp 108–131 °C (0.3–0.4 mm); n^{25}_D 1.5342.

The oily product in 750 mL of Et_2O was treated with excess ethereal HCl, and the precipitated salt was triturated with two 100-mL portions of acetone. Filtration gave 15.2 g of crystalline salt which was recrystallized from 1.5 L of CH_3CN with concentration to a 750-mL volume. Prisms (9.78 g) separated which were recrystallized a second time from 200 mL of absolute EtOH with concentration to a 40-mL volume to give 8.10 g of **methyl (2-*exo*-3-*endo*)-8-methyl-2-(1*H*-2-pyrrolyl)-8-azabicyclo-[3.2.1]octane-3-carboxylate,** compound **39** of Table I.

The filtrate from recrystallization of 15.2 g of the salt above was concentrated, and the basic material was liberated with concentrated NH_4OH. The resulting 3.94 g of oil in 25 mL of MeOH was heated under reflux with 0.25 g of $NaOCH_3$ (N_2 atmosphere) for 1.5 h. Concentration of the mixture by warming in vacuo, addition of 1 mL of H_2O, and extraction with Et_2O gave 3.53 g of oil which, upon dilution with pentane, precipitated 1.27 g of **methyl (*exo,exo*)-8-methyl-2-(1*H*-2-pyrrolyl)-8-azabicyclo[3.2.1]octane-3-carboxylate.** Chromatography of the filtrate residue on eight preparative silica gel plates using two solvent passes of 2:2:46:50 *i*-$PrNH_2$–MeOH–$CHCl_3$–pentane gave 0.56 g more of this same epimer as the less polar of two significant bands. Recrystallization of the total 1.83 g twice gave 1.34 g of compound **38** of Table I. The NMR spectra of **38** and **39** confirmed that the pyrrole rings were attached at their 2 positions.

Mixture **40–41** was prepared as reported[8] except that the Grignard addition was done at −20 °C. The isomers were not separated.

Compounds **42** and **43** were prepared by reaction of 2-thienylmagnesium bromide (0.3 mol) with methyl 1-methyl-1,2,-5,6-tetrahydropyridine-4-carboxylate[18] (0.2 mol) according to the standard method. Distillation of the crude, basic, oily product (34 g) gave 18 g of starting material and 6.9 g of a mixture of **42** and **43**: bp 108–112 °C (0.5 mm); two spots by TLC [silica gel, *i*-$PrNH_2$–Et_2O (3:97)]. The 6.9 g of product was chromatographed on 26 silica preparative plates, giving 4.0 g of less polar isomer **42** and 1.8 g of more polar isomer **43**. Treatment of 0.3 g of the less polar isomer with 0.12 g of $NaOCH_3$ in 5 mL of MeOH at reflux for 18 h and isolation of the basic material gave 0.23 g of a roughly 15:1 mixture of more polar and less polar isomers, respectively. Separation of the major product by TLC and comparison by TLC, IR, and NMR showed that the less polar isomer **42** had been converted almost entirely to the more polar isomer **43**.

With the identity of the isomers thus established, the oily cis base, **42**, was converted to its HCl salt which formed prisms from acetone: mp 176–177 °C (intumescence). Anal. ($C_{12}H_{17}NO_2$·S·HCl) C, H, Cl. The oily trans base, **43**, formed an HCl salt as prisms from acetone: mp 188–189 °C (intumescence). Anal. ($C_{12}H_{17}NO_2$S·HCl) C, H, Cl.

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References and Notes

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