(*exo,exo*)-2-Aryltropane-3-carboxylic Esters, Hypoglycemic Agents with Accompanying Analgesic Activity

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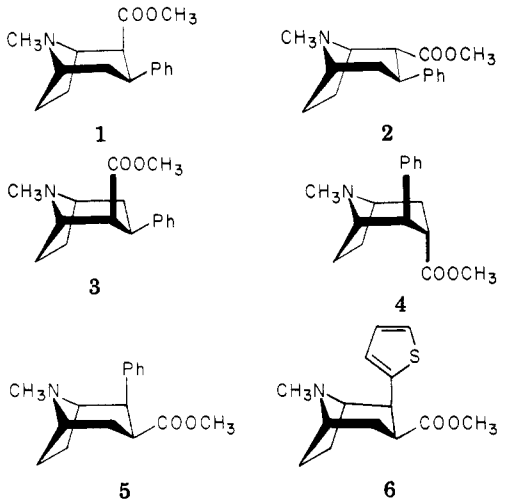
(*exo,exo*)-2-Aryltropane-3-carboxylic esters of types **6**, **7**, and **10** lower circulating blood glucose levels by 60–80%. This activity is accompanied by an analgesic activity roughly equal to that of codeine. Both of these activities reside in the 1*R* enantiomer and extensive structure–activity studies failed to separate them. The specific opioid antagonist nalorphine blocks the analgesic activity but does not diminish the hypoglycemic action. Conformational integrity afforded by the ethylene bridge is necessary for the observed activities.

An investigation of tropanes with an aromatic ring and a carboalkoxy group attached in various manners has revealed a surprising diversity of biological activities. Structures 1–6 indicate the absolute configurations of the



compounds involved. Compound 1 is a powerful stimulant,[1] whereas 2 produces no stimulation and is simply a local anesthetic about one-fifth as potent as cocaine.[2] The enantiomer of 1, compound 3, produces hyperglycemia.[3] In a reversal of the points of attachment of these groups, compound 4 is a pure narcotic antagonist lacking analgesic properties,[4] and 5 is a hypoglycemic agent. The thiophene analogue of 5, compound 6, is substantially more active than 5 in this respect, and both compounds demonstrate moderate analgesic properties. The present paper details the study of this hypoglycemic activity and attempts to separate it from the accompanying opiate-like action.

Biological Studies. The primary focus of the present work was on development of a useful hypoglycemic agent. Therefore, the corresponding analgesic screening was frequently run at a single, high-dose level simply to ascertain whether it was still present. Compound (±)-**6** was investigated more intensively than any other compound in the series. When it proved impossible to separate the two activities observed, the analgesic activity of (±)-**6** was evaluated carefully to determine if its profile might vary from that of usual opiates and perhaps be acceptable.

(±)-**6** was effective in lowering blood glucose levels in fasted rats, in glucose-loaded rats, and in rats given glucose and glucagon simultaneously (see Table I). The hypoglycemic action by the oral route appeared within 30 min and lasted approximately 1–1.5 h. While no attempt was made to determine the potency of (±)-**6** relative to tolbutamide, the data presented indicate that they have the same order of activity. (±)-**6** differs, however, from tolbutamide in that it does not alter circulating insulin levels.[5] Its actual mode of action is not known.

Curiously, the hypoglycemic action of (±)-**6** was produced by the oral route but not subcutaneously. This observation suggested that the activity was produced by a metabolite formed in the liver or the gastrointestinal tract. The latter was precluded by the finding of normal activity intravenously. Furthermore, oral activity was blocked completely by prior administration of the microsomal enzyme inhibitor SKF 525-A. This metabolism did not involve ester hydrolysis since corresponding acids were inactive (compare **7** with **24** and **5** with **38**, Table II). Acid **24** was also inactive intravenously so it is not just a case of lack of oral absorption. N-Demethylation, however, appeared to offer an explanation. Demethylated product **7** (Table II) produced an 81% reduction in circulating blood glucose at 87 mg/kg po and was not blocked by SKF 525-A. Indeed, compound **7** was the major (and only identified) metabolite from 24-h urine specimens of rats fed (±)-**6**.

Comparison of the hypoglycemic effects produced by the optical antipodes of (±)-**6** revealed that the activity resided in the levorotatory form [(−)-**6**] which was shown to correspond to cocaine in absolute configuration (1*R*). The dextrorotatory form was inactive at 100 mg/kg.

In addition to its hypoglycemic properties, compound (±)-**6** produced positive reactions in standard analgesic screening tests. It showed an ED_{50} of 100 ± 15 mg/kg sc and 83 ± 14 mg/kg po in the D'Amour–Smith rat tail-flick test. Note the activity by both routes here while the hypoglycemic activity was observed by the oral route alone. CNS effects were apparent above 100 mg/kg with severe convulsions and 5 out of 18 rats dead at 240 mg/kg sc. The ED_{50} for (−)-**6** (1*R*) was 59 ± 12 mg/kg po, whereas (+)-**6** (1*S*) appeared to have minimal activity (see Table II). Thus, the levorotatory isomer showed both the hypoglycemic and the analgesic properties, and we failed to accomplish a much desired separation of activities. The analgesic activity of these compounds at 120 mg/kg sc was completely blocked by a 1 mg/kg sc dose of the specific opioid antagonist nalorphine administered 10 min before the drug. It is of considerable interest that nalorphine blocked only the analgesic activity of these compounds and did *not* diminish their hypoglycemic action. SKF 525-A blocked both activities.

The ED_{50} of (±)-**6** against acetylcholine-induced (AcCh) writhing in mice was 12 mg/kg sc and 35 mg/kg po. In a more definitive test for analgesia than the latter, (−)-**6** was found to block the intraarterial bradykinin-evoked

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Table I. Effects of (±)-6 on Blood Glucose Levels of Fasted Rats, Fasted Rats Given Glucose, and Fasted Rats Given Glucose and Glucagon

treatment of fasted rats	oral dose, mg/kg	blood glucose, mg/100 mL ± SE, at postmedication hour 0	0.5	1	1.5	2
untreated		75 ± 2[a]	66 ± 2	66 ± 1	73 ± 4	75 ± 4
(±)-6	88	75 ± 2	36 ± 4	41 ± 6	53 ± 5	57 ± 5
% change[b]			−45	−38	−27	−24
untreated		74 ± 2	85 ± 2	92 ± 3	95 ± 4	92 ± 4
tolbutamide	50	74 ± 2	56 ± 2	55 ± 2	54 ± 2	58 ± 2
% change			−34	−40	−43	−37
glucose alone[c]		76 ± 2	149 ± 13	172 ± 9	130 ± 9	99 ± 2
glucose[c] + (±)-6	88	75 ± 2	67 ± 9	78 ± 6	88 ± 3	100 ± 8
% change			−55	−55	−32	
glucose alone[c]		74 ± 2	176 ± 8	183 ± 7	137 ± 8	131 ± 3
glucose[c] + tolbutamide	50	73 ± 2	172 ± 8	110 ± 5	64 ± 4	65 ± 2
% change				−40	−53	−50
glucose[c] + glucagon[d]		75 ± 2	211 ± 18	233 ± 15	135 ± 3	102 ± 7
glucose[c] + glucagon[d] + (±)-6	88	76 ± 2	80 ± 4	138 ± 20	105 ± 4	104 ± 7
% change			−62	−38	−22	

[a] Values are means ± SE for an eight-rat group. [b] All differences indicated are from control and are significant, $p < 0.01$ or better. [c] Glucose, 3 g/kg orally. [d] Glucagon, 3 mg/kg subcutaneously.

response in rats with an ED_{50} of 6.9 mg/kg po. Although (±)-6 was only about one-third as potent as codeine (49, Table II) in the AcCh writhing test, it was approximately equipotent with codeine in the tail-flick test. Only the levorotatory form of 6 was compared directly with codeine in the bradykinin test; it was more than 10 times as active. The time–effect relationships of (−)-6 and codeine in the latter test were vastly different as can be seen in Figure 1. All doses of (−)-6 exhibited a rapid onset and early offset of action, whereas the activity of the codeine dose shown was slow in developing but was sustained at peak effect up to 120 min. The time–response pattern for (−)-6 in Figure 1 gave credence to the earlier decision to switch from a 60-min to a 15-min reading time in the tail-flick test.

Chronic administration of (±)-6 in the rat did not induce physical dependence of the narcotic or narcotic-antagonist type. No abstinence signs were seen after abrupt withdrawal from (±)-6 infusion doses up to its maximum tolerated dose. No abstinence signs were seen after the attempted precipitation of withdrawal with naloxone challenge doses as high as 100 mg/kg. Consistent with its inability to induce physical dependence itself, (±)-6 did not support morphine physical dependence. Substitution of (±)-6 for morphine in morphine-dependent rats neither suppressed nor exacerbated morphine-withdrawal abstinence at (±)-6 substitution doses up to 32 times the morphine dose they replaced.

In rats (±)-6 produced catelepsy with an ED_{50} of 18.6 (12.1–40.3) mg/kg po. A dose of 32 mg/kg po produced catelepsy in 13 of 20 rats, but when 0.1 mg/kg sc of naloxone hydrochloride was given 15 min prior to the (±)-6, none of 10 rats in another group showed catalepsy ($p < 0.001$). A single dose of morphine conferred cross tolerance to a subsequent dose of (±)-6 given a day later in this catelepsy test (see Table III).

Compound (±)-6 also produced the Straub reaction in mice with an ED_{50} of 138 (94–192) mg/kg po. A dose of 300 mg/kg po produced the reaction in all of nine mice tested, but when 0.4 mg/kg sc of naloxone hydrochloride was given immediately before (±)-6, none of 10 mice tested showed Straub tails ($p < 0.001$).

Respiratory depression was produced by (±)-6 in two dogs. A 100 mg/kg im dose reduced the pulmonary ventilation rate of one animal by 40% within 20 min, but it was restored to normal within 1 min by 1 mg/kg iv of nalorphine. Development of tolerance to this respiratory effect was remarkable in that 4 h later a 150-mg/kg im dose of (±)-6 had no effect on the dog. A second dog showed a 65% drop in ventilation rate within 5 min and stopped breathing 3 min later. It was fully restored by nalorphine as above and also was unaffected by a later 150 mg/kg dose.

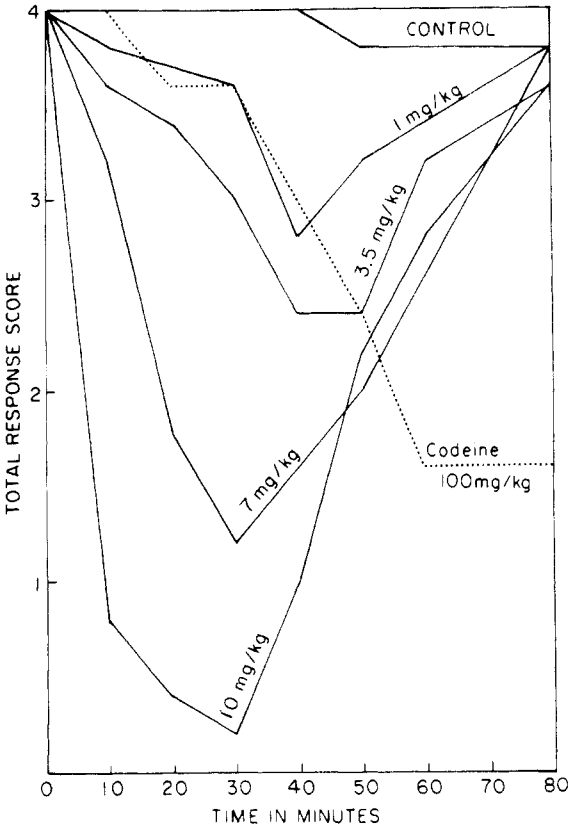


Figure 1. The effect of (−)-6 on bradykinin-induced response. See Experimental Section (Biological) for details of the test method. Each dose-level curve represents five rats medicated orally. Doses are calculated as free base.

Dose levels of (−)-6 of 120 mg/kg po or higher in rats produced tremors, rigidity, convulsions, and some deaths (see Table II). These toxic manifestations were much more apparent in the fasted animals used in the analgesic and hypoglycemic tests than in the glucose-loaded animals used in most of the hypoglycemic studies. Lengthening and branching the alkyl chain on the tropane nitrogen (compounds 8–12 of Table II) revealed that the *n*-amyl (10) and 2-ethylbutyl (12) compounds produced the greatest

glucose reduction. Table IV records the activity of **10** in the three hypoglycemic tests used earlier with **6**. Its activity equaled that of (±)-**6** but it showed *no* signs of toxicity at 240 mg/kg po. Compound **10** showed only a 71% response at 240 mg/kg po in the tail-flick test and an ED_{50} of 17 mg/kg po in the bradykinin test. Its activity in the tail-flick test was completely reversed by nalorphine.

In parallel with (±)-**6**, the hypoglycemic action of **10** was unaffected by nalorphine. It was an attractive possibility that nalorphine, a slightly more bulky molecule than **6** or **10**, might block these compounds from the opiate receptor site but that nalorphine might be too bulky to be adsorbed at the hypoglycemic receptor. This explanation was discounted when it was found that **4**, a narcotic antagonist[4] and of essentially the same size as **6**, also blocked the opiate aspects of **10** and not its hypoglycemic action.

As was the case with (±)-**6**, SKF 525-A blocked the hypoglycemic action of **10**. An assay of 24-h urine specimens of rats fed **10** indicated that deamylation had occurred. Metabolite **7** was detected by TLC and confirmed by mass spectrometry.

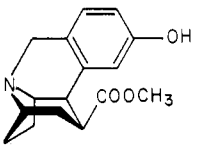
Turning now to the effect of other molecular modifications, the variety of substituents on the tropane nitrogen shown in compounds **13**–**22** (Table II) either failed to give hypoglycemic action or still produced analgesia. The hypoglycemic activities of cyanoethyl compound **20** and hydroxyethyl compound **15** were not blocked by SKF 525-A, but ethoxyethyl compound **17** was blocked.

Simply converting (±)-**6** to the corresponding ethyl ester destroyed hypoglycemic activity at the 100 mg/kg level (**26**) and adding one more methylene (**28**) caused the analgesia to disappear at the 240 mg/kg level. The 5-carbon ester **29** was likewise inactive as were the free carboxylic acids **24** and **38**. Moving the ester function to the endo configuration [(±)-**4**] gave a narcotic antagonist[4] which displayed no hypoglycemic activity. An acetyl group in place of the ester function at carbon-3 gave weak analgesic antagonist activity when a phenyl group was at C-2 (**39**), but analgesic activity was present with a thienyl at C-2 (**30**). Attachment of the thienyl group by its 3 position (**31**) or replacement of it by 2-(1*H*-pyrrolyl) (**32**) or by CH_3 (**33**) produced nothing of interest.

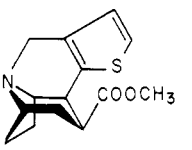
The initial discovery of hypoglycemic activity among the tropane esters was made with that ester carrying a phenyl instead of a thienyl group on carbon-2. None of these 2-phenyl compounds (**5** and **34**–**43**) showed outstanding activity. As expected, the hypoglycemic activity of nor compound **34** was not blocked by SKF 525-A. A nonparallelity was noted in the phenyl vs. the thienyl series when another position was varied. With a methyl on the nitrogen, the 2-thienyl compound (±)-**6** produced a 63% lowering of the glucose level, while the 2-phenyl compound (±)-**5** produced only a 24% drop. A benzyl group on the nitrogen in the 2-thienyl series (**13**) destroyed activity while the corresponding compound in the 2-phenyl series (**36**) produced a 42% drop.

The presence of a cyclopropylmethyl group on the nitrogen produced a change in opioid activity from that of agonist to antagonist. Compound **35** showed an AD_{50} of 4.7 mg/kg sc against phenazocine in the tail-flick test. Any interest in this compound as a hypoglycemic agent was diminished, however, by its CNS side effects.

The process of demethylation of tropanes carrying certain substituents on carbon-2 by means of the reagent diethyl azodicarboxylate[6] resulted in byproducts such as **45** and **46**. Details of the reactions involved are reported separately,[6] but both of these bridged substances showed hypoglycemic activity. Compound **46** was about three



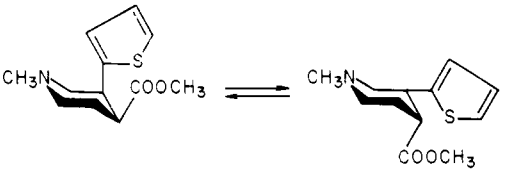
45



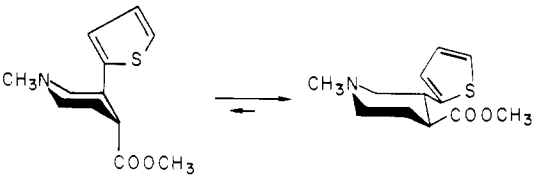
46

times as active in this respect as (±)-**6** but also much more toxic (see Table II). This hypoglycemic action was not blocked by SKF 525-A. Hypoglycemia was evident within 15 min and terminated in less than 90 min. The *N*-oxide (**47**) and a quaternary salt (**48**) of **46** were both inactive.

The rigidity of the tropane skeleton, imparted to the piperidine-ring moiety by an ethylenic bridge, was a requirement for the stimulant and narcotic-antagonist activities noted with other tropane esters.[1,4] In the present case two piperidines, **49** and **50**,[4] were studied in order to



49 (cis)



50 (trans)

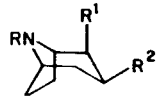
determine such requirements. In the test system employing glucose and glucagon, 87 mg/kg po of **49** caused a 30% elevation of the glucose level. Compound **50** at the same dose level caused a 40% elevation. Therefore, the intact tropane skeleton is also imperative for hypoglycemic activity.

In summary, some tropane esters have been found which are quite effective orally in reducing blood glucose levels with a duration of action approximating that needed for glucose control following meals. Unfortunately, this action is accompanied by an apparent analgesic effect which, even with evidence of low addiction liability, may well be undesirable on a continuing basis. There was also evidence of respiratory depression although this test was not done on amyl derivative **10**, the compound with the most favorable toxicity profile. It was not found possible to remove the analgesic side effects by structure modification nor was it possible to keep the analgesic property and eliminate the hypoglycemic effect. It was possible, however, to block the analgesic effects with a narcotic antagonist without affecting the substantial hypoglycemic activity.

Chemical Studies. The preparation of Table II compounds (±)-**5** and (±)-**6** is reported in an accompanying paper.[4] For the present study (±)-**6** was resolved using (−)-diisopropylidene-2-keto-L-gulonic acid monohydrate[7] to precipitate the levorotatory enantiomer and (+)-dibenzoyltartaric acid to separate the dextrorotatory form from the mother liquors. Surprisingly, the precipitate of the gulonic salt of (−)-**6** contained 2 mol of acid per mole of base. The characteristics of these enantiomers and their salts are summarized in Table V.

Absolute configurations were assigned to (+)- and (−)-**6** via preparation of one of them, (+)-**6**, from unsaturated ester **51** of known 1*S* configuration[8] (see eq 1).

Table II. Hypoglycemic and Analgesic Activities



compd	R	R¹	R²	hypoglycemic test dose[a]	% glucose redn[b]	tail-flick effect[c]	AcCh writhing, ED_{50}, mg/kg[c]	observations[d]
(±)-5[e]	CH_3	Ph	$COOCH_3$	88	24[f]	I, 120 sc[g]	12 (7.8-17)[h]	trem, 120 sc, R; sed, 40 sc, M
(−)-5[i]	CH_3	Ph	$COOCH_3$			lethal, 240 po[j,k]	18 (12-28)[h]	conv, 5/6 dead, 240 po, R
(+)-5[i]	CH_3	Ph	$COOCH_3$			59%, 240 po[j]	11 (7.2-16)[h]	trem, 240 po, R
(±)-6[e]	CH_3		$COOCH_3$	88	63[f]	29 ± 3.1 po[l] 83 ± 14 po[j]	12 (6.2-24)[h] 35 (26-44)[m]	sev conv, 5/18 dead, 240 sc, R
(−)-6[e]	CH_3		$COOCH_3$	88	75[f]	60 ± 8 sc[g] 59 ± 12 po[j]		3/18 dead, rigid, hypex, 120 po, R; bradykinin ED_{50} 6.9 (4.3-10) po, R
(+)-6[e]	CH_3		$COOCH_3$	88	I[f]	62%, 240 sc[g] 26%, 120 po[j]		conv, 1/6 dead; trem, rigid, 240 sc, R
7[e]	H		$COOCH_3$	87	81[f]	43 ± 3.3 po[j]	3.3 (2.2-5.0)[h]	stim, Straub tail, 150 po, M
8[e]	$(CH_3)_2CH$		$COOCH_3$	89	40[n]	87%, 240 po[l]	13%, 25[h]	conv, 240 po, R
9[i]	n-C_4H_9		$COOCH_3$	100	34[n]	88%, 240 po[l]	20%, 25[h]	
10[o]	n-C_5H_{11}		$COOCH_3$	100	60[f]	71%, 240 po[l]	57 (43-72)[m]	no side effects seen at 240 po, R; bradykinin ED_{50} 17 (8.4-39) po, R
11[i]	n-C_7H_{15}		$COOCH_3$	100	40[f]	70%, 240 po[j]	27%, 75[h]	sl rigid, stiff tails, jumpy, 480 po, R
12[i]	Et_2CHCH_2		$COOCH_3$	100	69[p]	72%, 240 po[l]	7%, 75[h]	tail-flick effect 24% at 15 min
13[i]	$PhCH_2$		$COOCH_3$	100	I[f]	I, 120 sc[g]	33%, 75[h]	
14[i]	$PhCH_2CH_2$		$COOCH_3$	100	29[n]	96%, 240 po[l]	27%, 75[h]	
15[e]	$HOCH_2CH_2$		$COOCH_3$	89	72[p]	100%, 240 po[l]	73%, 75[h]	rigid, hypex, conv, 240 po, R
16[q]	$HOCH_2(CH_2)_2$		$COOCH_3$	64	27[p]	92%, 240 po[l]	33%, 50[m]	rigid, trem, conv, 240 po, R
17[i]	$EtOCH_2CH_2$		$COOCH_3$	100	73[p]	100%, 240 po[l]	67%, 75[h]	hypex, rigid, trem, 240 po, R
18[i]	$(EtO)_2CHCH_2$		$COOCH_3$	100	47[n]	87%, 240 po[l]	27%, 75[h]	
19[i]	$CH_2(CH_2)_2OCHCH_2$		$COOCH_3$	100	39[n]	72%, 240 po[l]		

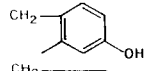
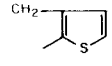
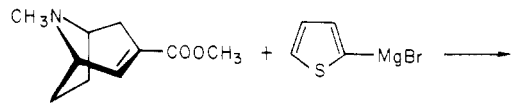
20[q]	$CNCH_2CH_2$		$COOCH_3$	64	64[p]	100%, 240 po[l]	60 (40-84)[m]	very rigid, 240 po, R
21[e]	CH_3OCOCH_2		$COOCH_3$	264	70[p,r]	100%, 240 po[l]	33%, 50[m]	
22[e]	NH_2COCH_2		$COOCH_3$	89	66[p]	72%, 240 po[l]	13%, 25[h]	rigid, 240 po, R
23[i]	$N(COOEt)HN(COOEt)CH_2$		$COOCH_3$	100	80[p]			
24[e]	H		COOH	78	I[n,s]			
25[e]	H		$COOC_2H_5$	88	66[p]	85%, 120 po[l]	2.8 (2.2-3.5)[h]	Straub tail, 2.5 sc, M; 3/6 dead, 80 sc, R
26[i]	CH_3		$COOC_2H_5$	100	I[f]	95 ± 12 po[l]	21 (17-26)[m]	stim, Straub tail, 150 po, M
27[i]	n-C_5H_{11}		$COOC_2H_5$	100	61[p]	65%, 240 po[j]	13%, 75[h]	
28[i]	CH_3		$COO(CH_2)_2CH_3$	100	I[f]	I, 240 po[j,l]	27%, 25[h]	
29[i]	CH_3		$COO(CH_2)_4CH_3$	100	I[f]	I, 240 po[j,l]	27%, 25[h]	
30[e]	CH_3		$COCH_3$	87	26[f]	55%, 240 sc[g]	12 (8.6-16)[h]	conv, trem, 2/6 dead, 240 sc, R; bradykinin 80% protected 50 sc, R
31[i]	CH_3		$COOCH_3$	300	42[f]	40%, 240 po[j]	12 (8.0-17)[h]	hypex, 240 po, R
32[i]	CH_3		$COOCH_3$	100	30[f]	86%, 480 po[j,t]	18 (13-24)[h]	trem, conv, 2/6 dead, 480 po, R; bradykinin ED_{50} 8.5 (0.63-43) po, R
33[e]	CH_3	CH_3	$COOCH_3$	84	I[p]			
34[e]	H	Ph	$COOCH_3$	87	31[f]	69%, 120 po[l]	4.0 (2.7-6.1)[h]	trem, hypex, 120 po, R
35[q]		Ph	$COOCH_3$	64	20[f]	I, 60 sc[g,u]	16 (12-20)[h]	hypac 2.5, trem, conv, 60 sc, R
36[i]	$PhCH_2$	Ph	$COOCH_3$	100	42[f]	60%, 480 po[j]	21 (16-28)[m]	trem, hypex, 480 po, R
37[e]	CH_3	Ph	$COOCH(CH_3)_2$	89	28[f]			
38[i]	CH_3	Ph	COOH	78	I[f]	I, 240 po[j,l]	7%, 75[h]	
39[e]	CH_3	Ph	$COCH_3$	87	32[f]	I, 120 sc[g,v]	7.0 (4.0-15)[h]	trem, 30 sc, conv, 120 sc, R
40[e]	CH_3	m-HO-Ph	$COOCH_3$	88	I[f]	I, 120 sc[g]	24 (17-34)[h]	inactive bradykinin, 100 sc, R
41[e]	H	m-HO-Ph	$COOCH_3$	88	I[f]	I, 240 po[j,l]	24 (15-35)[h]	
42[e]	CH_3	m-CH_3O-Ph	$COOCH_3$	89	24[f]			
43[i]	CH_3	p-HO-Ph	$COOCH_3$	100	I[f]			
44[e]	CH_3	$PhCH_2$	$COOCH_3$	88	21[f]	I, 120 sc[g]	5.8 (2.3-19)[h]	hypac, 75 sc, M; trem, 120 sc, R
45[i]			$COOCH_3$	100	33[p,w]			
46[e]			$COOCH_3$	9	43[f]	74%, 35 po[l,x]	1.5 (1.2-1.9)[h]	conv, 35 po, R; 15/15 dead, 75 sc, M
47[i]	N-oxide of **46**			94	I[p]	41%, 240 po[l,y]	67%, 50[m]	rigid, trem, 3/6 dead, 240 po, R

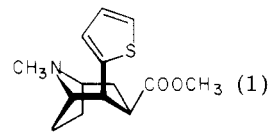
Table II (*Continued*)

compd	R	R¹	R²	hypoglycemic test dose[a]	% glucose redn[b]	tail-flick effect[c]	AcCh writhing, ED_{50}, mg/kg[c]	observations[d]
48[i]	ethyl quaternary of 46			100	I[f]			
49	codeine					112 po[j]	3.8 (2.9–4.6)[h] 11 (8.4–15)[m]	bradykinin ED_{50} 111 (75–230) mg/kg po, R

[a] Dose in mg/kg calculated as free base, administered orally; variation in dose size due to the use of a standard test dose of 100 mg/kg of salt at hand. [b] The test method is footnoted by each datum. Changes of < 20% are considered as inactive (I) since variations render such values not significant. [c] Dose (mg/kg) calculated as free base; values are ED_{50} with standard error or confidence limits (if not available, then % change). [d] Numbers refer to dosage in mg/kg; M = mice, R = rat, conv = convulsions, hypac = hyperactive, hypex = hyperexcitable, saliv = salivation, sed = sedation, sev = severe, sl = slight, stim = stimulation, trem = tremors. [e] HCl salt tested. [f] Glucagon-impaired glucose disposal test. [g] Postmedication observation time was 30 min. [h] Subcutaneous administration. [i] Free base tested. [j] Postmedication observation time was 60 min. [k] This enantiomer has a weak action as a narcotic antagonist; 73% at 80 mg/kg sc. [l] Postmedication observation time was 15 min. [m] Oral administration. [n] Test done on fasted rats. [o] Methanesulfonate salt tested. [p] Test done on glucose-loaded rats. [q] *p*-Methylbenzenesulfonate salt tested. [r] The compound was inactive at 88 mg/kg po in the glucagon-impaired glucose disposal test. [s] Also inactive at 78 mg/kg iv. [t] The response was 19% at 240 mg/kg po. [u] Compound showed antagonist activity, AD_{50} 4.7 (2.9–7.5) mg/kg sc. [v] Antagonist activity at 1 and 80 mg/kg sc but no dose–response pattern. [w] A 30-min reading. At 1 h there was no depression and at 1.5 and 2 h the glucose levels were elevated by 20%. [x] Tail-flick response was only 14% at 30 min and 12% at 60 min. [y] Tail-flick response was only 14% at 60 min.



51



(+)-6

Demethylation of (±)-6 to form nortropane 7 (Table II) presented special problems which were solved by use of diethyl azodicarboxylate as described in a separate publication.[6] Alkylation of 7 was then accomplished in conventional manners as described in the Experimental Section (Chemical) to give compounds 8–22 with the exception of 13. This *N*-benzyl compound was prepared from the (±)-*N*-benzyl analogue of 51 by the method of eq 1.

Hydrazine dicarboxylate derivative 23 together with compounds 46–48 were all prepared as described in ref 6. Compounds 32, 34, 36–38, 40–44, 49, and 50 are described in ref 4. Compound 33 is described in ref 8.

The variety of esters 25–29 was prepared by hydrolysis of the corresponding methyl esters, followed by acid-catalyzed esterification with the appropriate alcohol. Ketones 30 and 39 resulted from treatment of the corresponding 3-carbomethoxy compound with a limited amount of CH_3MgBr. A 3-thienyl analogue, 31, was prepared using 3-thienylmagnesium bromide which required an entrainment procedure (2 equiv of $BrCH_2CH_2Br$ and excess Mg) for its formation. Finally, exo ester 35 was made from its endo epimer[4] by treatment with $NaOCH_3$ in MeOH. Table V presents the characteristics of all new compounds described in this paper.

Experimental Section

I. Biological. Hypoglycemic Studies. Fasted, 100-g, male, Sprague–Dawley rats were given either H_2O or the test compound in water alone or with glucose (3 g/kg po) or with glucose plus glucagon (3 mg/kg sc). Blood samples were obtained from the tail vein at 0, 0.5, 1, 1.5, and 2 h after treatment and were analyzed for glucose using a Technicon auto analyzer.

In blocking experiments, SKF 525-A was administered at 20 mg/kg ip 45 min prior to the test compound. In the blocking experiments with nalorphine, 10 mg/kg of this drug was administered sc at the time of treatment with the compound undergoing testing.

Metabolic Study. Four, 200-g, male, Sprague–Dawley rats were medicated orally with 1 mL of 60% glucose solution, followed by 20 mg of the test compound (calculated as free base) in 0.5 mL of H_2O, and the dosing was repeated in 3 and 6 h. The animals were put in metabolism cages and the 0- to 24-h urine samples were collected and pooled. A 10-mL aliquot of the urine was extracted twice with 30 mL of CH_2Cl_2, and the residue from the extracts was dissolved in 5 mL of MeOH and transferred to a conical centrifuge tube. The MeOH was evaporated, the residue was dissolved in 200 μL of MeOH, and a 25-μL aliquot was spotted on a silica TLC plate. Development of the plate with 5:95 Et_3N–benzene revealed 4–5 Dragendorff-positive spots which were not present from the control group. Single spots were scraped and transferred to the mass spectrograph by the Clarke procedure.[9] The only compounds isolated in significant quantity were the administered drug and its N-dealkylated product.

Dependence Liability. (±)-6 was tested in Sprague–Dawley rats for physical dependence and for ability to substitute for morphine in morphine-dependent rats. Chronic drug administration for these tests was by continuous intraperitoneal infusion through an indwelling cannula, as described previously.[10] Physical dependence was tested by two withdrawal procedures. One procedure was the abrupt withdrawal of (±)-6 after 6 days of

Table III. Tolerance and Cross Tolerance Induced by a Single Injection of Morphine (Catalepsy Test)

pretreatment 24 h prior to testing	second treatment[a]	% cataleptic rats	no. of rats
none	morphine, 8 mg/kg sc	93	15
morphine, 128 mg/kg sc	morphine, 8 mg/kg sc	12[b]	8
none	(±)-6, 32 mg/kg po	65	20
morphine, 128 mg/kg sc	(±)-6, 32 mg/kg po	20[c]	10

[a] Morphine was administered 30 min prior to testing. (±)-6 was administered 15 min prior to testing. [b] Significant at $p < 0.001$ level. [c] Significantly different from control group at 0.05 level.

infusion at various 0.3 log interval doses up to its maximum tolerated dose of (800 mg/kg)/24 h. The second procedure was the precipitation of withdrawal with the narcotic antagonist naloxone after 2 days of (±)-6 infusion at the standard dose of (100 mg/kg)/24 h. Occurrence of abstinence signs after withdrawal would indicate that the animals had been physically dependent. The test conditions used, i.e., 6 days of infusion prior to abrupt withdrawal and 2 days of infusion at a dose of (100 mg/kg)/24 h prior to naloxone-precipitated withdrawal, demonstrate physical dependence for both narcotic and narcotic-antagonist reference analgesics.[11] For the substitution test, rats first were made physically dependent on morphine by infusion at a dose of (12.5 mg/kg)/24 h for 6 days. Morphine then was withdrawn and the infusion continued with (±)-6.

Analgesic Studies. Narcotic analgesia was determined in Sprague–Dawley rats by a modified D'Amour–Smith "tail-flick" method described by Harris and Pierson.[12] Oral tests were done on fasted rats; subcutaneous tests used fed rats. The effectiveness of nalorphine in blocking the administered drug was determined by administering 1 mg/kg of nalorphine sc 10 min prior to giving the drug. Narcotic antagonism was evaluated according to a procedure of these same investigators.[12] Antiwrithing activity (activity in preventing the abdominal constriction response) was measured in Swiss–Webster mice using acetylcholine (AcCh) as the inducing agent according to the procedure of Collier et al.[13] The capability of compounds to block the intraarterial bradykinin-evoked response in rats was determined by the methods of Deffenu et al.[14] and of Botha et al.[15] Confidence limits for the AcCh data were calculated by the method of Bliss;[16] standard errors for the tail-flick data were calculated by the method of Miller and Tainter.[17]

In the tail-flick agonist test it became evident that the compounds had a very rapid onset of action so, early in the study, the oral postmedication observation time was shifted from 60 to 15 min, with data in a few instances reported at both times. Note that (±)-6 is more than twice as active at 15 min than at 60 min (Table II). All animals which were medicated subcutaneously were tested after 30 min.

In the determination of the blocking action of SKF 525-A on the tail-flick agonist action of (±)-6, 20 mg/kg of SKF 525-A (or 0.9% saline in the control group) was given ip 45 min before the (±)-6. The effect was tested 15 min later.

Catalepsy Test.[18] Male, Sprague–Dawley rats of 90–120-g body weight were used for the test. Medication was administered orally 15 min before testing the animal. Dosage was calculated as milligrams per kilogram in terms of free base, and the drug concentration in water was adjusted so that 0.1 mL of solution was administered per 100 g of body weight.

The particular test procedure involved gently placing the rat with his forelimbs touching a horizontal rod which was 4 mm in diameter and elevated 8 cm above a surface. The rat's rear feet were positioned 9.5 cm from an imaginary perpendicular plane drawn from the rod to the surface. The rat was scored cateleptic if he held onto the rod for a consecutive 45 s during one of four successive test trials. If the rat moved from the rod before the 45-s cutoff, he was immediately given another trial up to a maximum of four trials.

The ED_{50} values and 95% confidence limits were computed by the method of Finney.[19] The statistical significance of the difference between groups was determined by the two-tailed Fisher exact probability test.[20]

Straub Reaction. The Straub tail ED_{50} was determined using male, Swiss–Webster mice according to the method of Aceto et al.[21] In the blocking of this reaction by naloxone, 0.1 mg/kg sc of the latter was given 30 min prior to testing.

Respiratory Depression. The effect of (±)-6 on respiratory rate (RR) and pulmonary ventilation rate (PVR) was examined in two anesthetized dogs using a Grass polygraph to record the parameters. The signal for the primary trace of respiratory rate and pattern was derived from a Grass pressure transducer to which a pressure differential proportional to the flow rate through a Fleisch pneumotachograph was introduced. The pneumotachograph was, in turn, connected to a tracheal cannula by means of a Digby-Leigh nonrebreathing valve such that only inspired air passed through the measuring system. Integration of the primary trace, from which the PVR was calculated, was performed by a Grass unit integrator and was recorded on a second channel.

Antagonism of Analgesic Action of 10 by Another Tropane, 4. Tropane 4 has an AD_{50} = 5.5 mg/kg sc as a narcotic antagonist.[4] When 50 mg/kg of 4 was administered sc 20 min before compound (±)-10 was given (240 mg/kg po) in the standard tail-flick test (reading in 15 min), 0/18 of the animals went to 20 s. In the control group given water instead of 4, 9/18 rats went to 20 s. In a second group given 4 and then only water 20 min later, 0/18 went to 20 s.

II. Chemical. Analytical results for indicated elements are within ±0.4% of the theoretical values on all new compounds reported. The NMR and IR spectra of all new compounds were compatible with their assigned structures. A Varian HA-100 spectrometer was used for the NMR spectra with Me_4Si as an internal standard. The standard method for Grignard reagent addition to α,β-unsaturated esters referred to in several experiments is detailed in ref 4. Preparative plate chromatography

Table IV. Comparison of 10 in Three Hypoglycemic Tests[a]

treatment	blood glucose, mg/100 mL ± SE, at postmedication hour 0	0.5	1.0	1.5	2.0
glucose (3 g/kg ig) + glucagon (3 mg/kg sc)					
control[b]	80 ± 2	204 ± 7	201 ± 16	169 ± 13	110 ± 10
10 present[c]	80 ± 2	82 ± 12	80 ± 7	81 ± 8	77 ± 6
% change		−60	−60	−52	
glucose-loaded rats (3 g/kg ig)					
control[d]	80 ± 2	188 ± 9	169 ± 10	119 ± 5	104 ± 4
10 present[c]	80 ± 2	62 ± 7	73 ± 10	80 ± 12	76 ± 7
% change		−67	−61	(−33)	
fasted rats					
control[e]	86 ± 2	82 ± 4	87 ± 3	89 ± 3	90 ± 2
10 present[c]	86 ± 2	48 ± 3	51 ± 4	55 ± 4	61 ± 5
% change		−42	−41	−39	−33

[a] All tests involved eight rats per group with an average body weight of 100 g. All % change values have $p < 0.001$ except the one in parentheses where $p < 0.01$. [b] Glucose plus glucagon and vehicle. [c] All doses of 10 were 100 mg/kg po. [d] Glucose plus vehicle. [e] Fasted rats given vehicle alone.

Table V. Chemical Data

compd	formula	mp or bp (mm), °C	$[\alpha]^{25}_D$, deg, or n^{25}_D	recrystn solvent	% yield	analyses
(−)-6	$C_{14}H_{19}NO_2S \cdot 2(C_{12}H_{18}O_7)$[a]	145–146	−36.5[b]	Et_2O		C, H, N, S
	$C_{14}H_{19}NO_2S$	106–107[c]	−70.1[d]	C_6H_{12}	71	C, H, S
	$C_{14}H_{19}NO_2S \cdot HCl$	213–215[c,e]	−70.7[f]	CH_3CN		C, H, Cl
(+)-6	$C_{14}H_{19}NO_2S \cdot C_{18}H_{14}O_8$[g]	174[h]	+106.8[i]	EtOH		C, H, S
	$C_{14}H_{19}NO_2S$	104–106.5[c]	+69.8[d]	C_6H_{12}	80	C, H, S
	$C_{14}H_{19}NO_2S \cdot HCl$	213–214[c,e]	+70.6[f]	CH_3CN		C, H, Cl
8	$C_{16}H_{23}NO_2S \cdot HCl$	230–231[e,j]		acetone	54	C, H, Cl
9	$C_{17}H_{25}NO_2S$	148–149.5 (0.3)	1.5322		79	C, H, S
10	$C_{18}H_{27}NO_2S$	147–149 (0.2)	1.5269		88	C, H, S
	$C_{18}H_{27}NO_2S \cdot CH_4O_3S$	112–115[k]				C, H, N
11	$C_{20}H_{31}NO_2S$	160–161 (0.15)	1.5205		70	C, H, S
12	$C_{19}H_{29}NO_2S$	147–149 (0.2)			67	C, H, S
13	$C_{20}H_{23}NO_2S$	138–140[c]		MeOH	19	C, H, S
14	$C_{21}H_{25}NO_2S$	85–86[l]		MeOH	90	C, H, S
15	$C_{15}H_{21}NO_3S \cdot HCl$	178–180[e,l]		CH_3CN	42	C, H, Cl
16	$C_{16}H_{23}NO_3S \cdot C_7H_8O_3S$	175–176[c]		CH_3CN	36[m]	C, H, S
17	$C_{17}H_{25}NO_3S$	62–65[c]		Et_2O-pentane	49	C, H, S
18	$C_{19}H_{29}NO_4S$	170–172 (0.35)			37	C, H, S
19	$C_{18}H_{25}NO_3S$	165–167 (0.2)			75	C, H, S
20	$C_{16}H_{20}N_2O_2S \cdot C_7H_8O_3S$	209–211[c]		CH_3CN	63	C, H, S
21	$C_{16}H_{21}NO_4S \cdot HCl \cdot 0.5H_2O$	155–156.5[n]		acetone	46	C, H, S
22	$C_{15}H_{20}N_2O_3S \cdot HCl$	233[e]		CH_3CN-EtOH	53	C, H, S
24	$C_{12}H_{15}NO_2S \cdot HCl \cdot {}^1/_3EtOH$	189–190[c,e]		EtOH	47	C, H, Cl
25	$C_{14}H_{19}NO_2S \cdot HCl$	267–268[c,h]		EtOH	75	C, H, S
26	$C_{15}H_{21}NO_2S$	123–126[o] (0.1)	1.5380		72	C, H, S
27	$C_{19}H_{29}NO_2S$	149–153[o] (0.2)			82	C, H, S
28	$C_{16}H_{23}NO_2S$	136–150[o] (0.3)	1.5330		73	C, H, S
29	$C_{18}H_{27}NO_2S$	167–170 (0.4)	1.5245	CH_3CN	26	C, H, S
30	$C_{14}H_{19}NOS$	110.5–112[c]		C_5H_{12}	22	
	$C_{14}H_{19}NOS \cdot HCl$	246–247[h,n]		CH_3CN		C, H, S
31	$C_{14}H_{19}NO_2S$	144–145 (0.8)	1.5458		63	C, H, N
35	$C_{19}H_{25}NO_2 \cdot C_7H_8O_3S$	173–176[o]		acetone	69[m]	C, H, S
39	$C_{16}H_{21}NO \cdot HCl$	215–216[c,h]		CH_3CN	37	C, H, Cl

[a] (−)-Diisopropylidene-2-keto-L-gulonic acid salt. [b] 1% in EtOH. [c] Prisms. [d] 1% in $CHCl_3$. [e] Intumescence. [f] 1% in H_2O. [g] Dibenzoyltartrate salt. [h] Decomposition. [i] 1% in pyridine. [j] Blades and plates. [k] Salt was prepared in *i*-PrOAc from which it precipitated in pure form. [l] Blade clusters. [m] Yield of base. [n] Plates. [o] Needles.

was done with Brinkmann PF_{254} silica gel in 1–1.5-mm thickness on 20 × 40 cm glass plates. Melting ranges were determined in capillary tubes and are uncorrected.

Resolution of Methyl (1*RS*-*exo*,*exo*)-8-Methyl-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate [(±)-6]. To a solution of 58.5 g (0.20 mol) of (−)-diisopropylidene-2-ketogulonic acid monohydrate in 2.8 L of Et_2O was added 26.3 g (0.099 mol) of (±)-6. The solution was boiled down to a 400-mL volume, and the precipitate was collected at room temperature and washed with 25 mL of Et_2O: 40.0 g; mp 141–143.5 °C. This solid was recrystallized from 2.5 L of Et_2O boiled down to a 125-mL volume to give 35.3 g of a salt containing one molecule of (−)-base and *two* molecules of the (−)-gulonic acid, mp 144–145.5 °C, and a second crop of 1.8 g of the same melting point: total yield 37.1 g, 92%. Another recrystallization gave the material entered under (−)-6 in Table V.

The (−)-base was liberated from this gulonate salt with 2 N NaOH and extracted with Et_2O. Addition of Et_2O·HCl to this extract, trituration of the precipitated HCl salt with acetone, and recrystallization from CH_3CN gave 9.4 g (three crops) of (−)-6·HCl. A second recrystallization from CH_3CN gave 8.3 g of the HCl salt entered under (−)-6 in Table V.

The total mother liquors from purification of the initially precipitated 40.0 g of (−)-base salt above were treated with base to collect the remaining impure (−)-base (2.5 g). A solution of this base in 10 mL of warm absolute EtOH was added to a solution of 3.54 g of (−)-dibenzoyltartaric acid monohydrate in 40 mL of absolute EtOH, and the precipitated salt was collected at 25 °C: 5.6 g; mp 175 °C dec. This salt was treated with 7 mL of 2 N HCl, the liberated acid was extracted with ether, and the aqueous layer was made basic with concentrated NH_4OH. The liberated (−)-base (2.3 g) was recrystallized from cyclohexane to give 2.06 g of massive prisms of (−)-6 base (Table V).

The ethereal filtrate from separation of the 40 g of (−)-base salt was treated with 70 mL of 2 N NaOH and the layers were separated. The aqueous layer was extracted once with Et_2O, and the Et_2O layers were concentrated to give 12.7 g of impure, crystalline (+)-6 base. It was dissolved in 50 mL of warm absolute EtOH and added to a warm solution of 18.0 g of (+)-dibenzoyltartaric acid in 200 mL of absolute EtOH. The precipitated salt was collected at room temperature and washed with two portions of EtOH to give 28.1 g of the dibenzoyltartrate salt listed under (+)-6 in Table V.

The 28.1 g of salt was converted to the free base using the method just described for (−)-6, giving 11.66 g of (+)-6, mp 97–104 °C. Recrystallization from cyclohexane afforded 10.7 g of the material described in Table V. Its HCl salt is also listed there.

Reaction of (−)-51 (1*S* Configuration) with 2-Thienylmagnesium Bromide. A solution of 1.24 g (0.0069 mol) of (−)-51[8] in 10 mL of Et_2O was added in 10 min with stirring to a Grignard reagent [prepared from 2.0 g (0.012 mol) of 2-bromothiophene and 0.50 g (0.021 g-atom) of Mg in 15 mL of Et_2O] held at −20 °C. A gum precipitated on the flask wall. The mixture was stirred for 15 min at −20 to −25 °C and then poured into 20 mL of 2 N HCl and 50 g of ice. This mixture was poured back into the reaction flask to complete the quench. Nonbasic components were washed away with Et_2O and the water layer was made basic with concentrated NH_4OH. The 1.54 g of oily base liberated was dissolved in 5 mL of MeOH, 0.1 g of $NaOCH_3$ was added, and the solution was heated under reflux under N_2 for 2 h. Removal of the MeOH in vacuo, addition of water, and extraction with Et_2O gave 1.2 g of crystalline base. Purification on five 20 × 40 cm silica gel chromatoplates using 2:20:78 *i*-$PrNH_2$–Et_2O–pentane afforded 0.89 g (49%) of (+)-6 which contained no 3α epimer. Recrystallization from cyclohexane gave 0.66 g of massive prisms: mp 86–103 °C; $[\alpha]^{25}_D$ +56.3° (1% in $CHCl_3$).

In order to obtain optically pure material, the base (0.83 g) in 3 mL of absolute EtOH was added to a solution of 1.18 g of (+)-dibenzoyltartaric acid in 5 mL of absolute EtOH. The precipitated salt (1.67 g) was treated with excess 2 N HCl, the liberated acid was removed with Et_2O, and the aqueous layer was basified with concentrated NH_4OH. Extraction with Et_2O in-

volved a major spill. The recovered base was recrystallized from cyclohexane to give massive prisms of (+)-6: mp 105–106 °C; $[\alpha]^{25}_D$ +67.9° (1% in $CHCl_3$).

Compound 8, **methyl (*exo,exo*)-8-(2-propyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared by stirring a mixture of 5.02 g (0.020 mol) of **methyl (*exo,exo*)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate (7),**[6] 5.04 g (0.060 mol) of solid $NaHCO_3$, 6.80 g (0.040 mol) of 2-iodopropane, and 35 mL of dry DMF at room temperature for 3 days. Silica TLC (3:97 *i*-$PrNH_2$–Et_2O) showed incomplete reaction. More isopropyl iodide (6.8 g) and $NaHCO_3$ (5 g) were added and the mixture was heated at 60–70 °C with stirring for 9 h. TLC showed complete reaction. The DMF was removed by warming in vacuo, water was added, and the mixture was extracted twice with Et_2O. Addition of ethereal HCl precipitated a gum which crystallized upon trituration with Et_2O. One recrystallization of the resulting 5.1 g of salt gave 3.55 g of compound 8 (Table V).

Compound 9, **methyl (*exo,exo*)-8-(1-butyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared from 1-iodobutane and 7 by the method used for 8 except that the reaction was complete at room temperature in 21 h without addition of further reagents. When the precipitated HCl salt failed to crystallize, it was treated with concentrated NH_4OH, and the liberated base was extracted with Et_2O and distilled to give pure 9 as an oily base.

Compound 10, **methyl (*exo,exo*)-8-(1-pentyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared from 1-iodopentane and 7 by the method used for 9. Following distillation of the product, it was found possible to prepare a crystalline methanesulfonate salt.

Compound 11, **methyl (*exo,exo*)-8-(1-heptyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared from 1-iodoheptane and 7 in the same way as for 9 except that the reaction was run at 60 °C in 3 h.

Compound 12, **methyl (*exo,exo*)-8-[1-(2-ethylbutyl)]-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared by stirring a mixture of 4.0 g (0.016 mol) of 7, 4.2 g (0.05 mol) of solid $NaHCO_3$, 5.28 g (0.032 mol) of 3-(bromomethyl)-pentane, and 25 mL of DMF at room temperature for 65 h. TLC [silica gel, *i*-$PrNH_2$–Et_2O (3:97)] showed only about 30% reaction. It was then heated at 60 °C for 48 h whereupon it showed greater than 90% reaction. The mixture was concentrated by warming in vacuo, Et_2O was added, and the mixture was filtered. The filtrate yielded 6.4 g of oil which was chromatographed on basic alumina to remove the starting material. The resulting 4.13 g of oil was distilled to give 3.57 g of pure compound 12.

Compound 13, **methyl (*exo,exo*)-8-(phenylmethyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared from methyl 8-(phenylmethyl)-8-azabicyclo[3.2.1]oct-2-ene-3-carboxylate[4] (38.5 g, 0.150 mol) and 2-thienylmagnesium bromide (0.22 mol) by the standard method of ref 4. Distillation of the basic material isolated gave a forerun of 20.4 g collected at 136–182 °C (0.5 mm), most of which was starting material (50% recovery). The desired product was collected rapidly at 182–196 °C (0.5 mm) as a mixture, epimeric at C-3 (13.1 g, 26%).

Conversion of the mixture to the 3-exo epimer was done by refluxing the 13.1 g of mixture in 50 mL of MeOH containing 0.5 g of $NaOCH_3$ for 2 h. Massive prisms precipitated during the process. The solvent was removed in vacuo, and the residue was treated with 75 mL of CH_2Cl_2, 75 mL of Et_2O, and 5 mL of H_2O in that order and shaken. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give 12.6 g of crystalline solid. Two crystallizations gave 9.65 g of compound 13 (Table V).

Compound 14, **methyl (*exo,exo*)-8-(2-phenylethyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared from 2-phenylethyl bromide and 7 by the method used for 9. When stirring at room temperature for 66 h produced only about 80% reaction, the mixture was heated at 70 °C for 5 h to complete it. The HCl salt of the product failed to crystallize. The liberated base, however, did crystallize and was recrystallized twice from MeOH to give 14 (Table V). The yield is based upon once recrystallized material of nearly the same melting point (85–87 °C).

Compound 15, Methyl (*exo,exo*)-8-(2-Hydroxyethyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate. Compound 7 (4.0 g, 0.012 mol) was added to a solution of 10 g (0.23 mol) of ethylene oxide and 1.6 g (0.017 mol) of phenol in 75 mL of CH_3CN, and the solution was heated in an autoclave for 6 h at 125 °C. The mixture was concentrated by warming in vacuo and the residue was extracted with Et_2O. The basic product was extracted from the Et_2O with 2 N HCl and liberated with concentrated NH_4OH. A solution of the basic product in Et_2O was treated with gaseous HCl and the gummy precipitate was triturated with acetone to give a crystalline salt. Two recrystallizations from CH_3CN furnished pure compound 15.

Compound 16, **methyl (*exo,exo*)-8-(3-hydroxypropyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared, starting with 4.0 g (0.016 mol) of 7, 4.2 g (0.05 mol) of solid $NaHCO_3$, 25 mL of DMF, and 5.80 g (0.032 mol) of 3-bromopropyl acetate. The mixture was stirred for 22 h at room temperature and filtered, and the residue from concentration of the filtrate was purified by chromatography on 20 silica preparative plates (3:97 *i*-$PrNH_2$–Et_2O).

The resulting 5.0 g of the 8-(3-acetoxypropyl) intermediate was dissolved in 70 mL of 2 N HCl, and the solution was heated under reflux for 24 h. Concentration by warming in vacuo gave 4.6 g of **(*exo,exo*)-8-(3-hydroxypropyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid.** A solution of the latter in 50 mL of MeOH was saturated with gaseous HCl and refluxed gently for 4 h with a slow stream of HCl bubbling into it. Concentration of the mixture by warming in vacuo, treatment with concentrated NH_4OH, and ether extraction gave 2.55 g of basic oil which was about 80% pure by TLC. It was chromatographed as above on 10 plates to give 1.80 g of 16 base. One recrystallization of the *p*-toluenesulfonate salt gave compound 16 (Table V).

Compound 17, **methyl (*exo,exo*)-8-(2-ethoxyethyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared from 4.9 g (0.032 mol) of 2-bromoethyl ethyl ether and 4.0 g (0.016 mol) of 7 in the same way as for 9 except that the reaction mixture was heated at 60 °C for 7 h. It was diluted with Et_2O and filtered, and the filtrate was concentrated by heating in vacuo. The residue was dissolved in 50 mL of Et_2O, and the solution was filtered free of a brown gum (0.3 g) and concentrated to a 10-mL volume. Addition of 20 mL of pentane and chilling caused precipitation of 1.85 g of 17. A second crop (0.7 g) of equal purity was obtained.

Compound 18, **methyl (*exo,exo*)-8-(2,2-diethoxyethyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared from 4.0 g (0.016 mol) of 7 and 6.31 g (0.032 mol) of α-bromoacetaldehyde diethyl acetal in the same way as for 9 except that the mixture was heated at 90–100 °C for 4 h. The product distilled at 170–172 °C (0.35 mm), 3.52 g. The particular sample of 7 used contained some diethyl hydrazodicarboxylate byproduct as an impurity which codistilled with the present product (IR peak at 1675 cm^{-1} for the impurity).

The product was precipitated from Et_2O with gaseous HCl and the base recovered with 5 N NH_4OH to remove most of the impurity, but chromatography on basic alumina (1:9 EtOAc–hexane) was used for final purification. Pumping the resulting oil at 80–85 °C gave 2.15 g of pure 18.

Compound 19, **methyl (*exo,exo*)-8-tetrahydrofurfuryl-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared from 5.02 g (0.020 mol) of 7 and 6.6 g (0.040 mol) of tetrahydrofurfuryl bromide[22] by the method used for 8. Stirring for 65 h at 25 °C produced negligible reaction. When heating at 80 °C for 24 h produced only 50% reaction, an additional 6.6 g of bromide and 5 g more $NaHCO_3$ were added and heating at 80 °C was continued for 15 h. With apparent 95% reaction, the mixture was diluted with 10 mL of H_2O and extracted twice with Et_2O. The extracts were washed with brine and concentrated to give 6.34 g of oil which was treated with 10 mL of Ac_2O for 15 min. This solution was concentrated, the residue was dissolved in Et_2O, and the basic component was precipitated with HCl. Treatment of the gummy salt with concentrated NH_4OH, separation of the base with Et_2O, and distillation of this product afforded 5.03 g of 19, bp 160–167 °C (0.2 mm), most of which boiled at 165–167 °C.

Compound 20, **methyl (*exo,exo*)-8-(2-cyanoethyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared by refluxing a solution of 4.0 g (0.016 mol) of 7 in 15 mL of acrylonitrile for 72 h. TLC [silica, *i*-$PrNH_2Et_2O$ (3:97)] indicated

that reaction was about 95% complete. The solution was concentrated to a residue which was chromatographed on silica preparative plates to give 3.5 g of pure **20** base. It was converted in EtOAc to a *p*-toluenesulfonate salt, compound **20** (Table V).

Compound 21, Methyl (*exo,exo*)-3-(Methoxycarbonyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-8-acetate. A mixture of 3.32 g (0.010 mol) of **7**·HBr, 4.0 g (0.048 mol) of solid $NaHCO_3$, and 25 mL of DMF was heated to 100 °C with stirring, and a solution of 3.06 g (0.020 mol) of methyl bromoacetate in 10 mL of DMF was added in 1-mL portions over a period of 10 min. Gas was evolved. The mixture was stirred and heated thus for 1 h, and the DMF was then distilled in vacuo.

The residue was treated with 10 mL of 2 N NaOH and extracted twice with Et_2O. Addition of HCl to the extracts precipitated a salt which crystallized upon trituration with acetone in which the crystalline salt is only slightly soluble. A mechanical loss occurred and the process of recovery involved MeOH which rendered the salt again amorphous. It was dissolved in 100 mL of hot acetone, and the hot solution was filtered and concentrated to a 25-mL volume. Pure **21** (1.70 g) crystallized as a hemihydrate.

Compound **22**, **[*exo,exo*)-3-(methoxycarbonyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-8-acetamide,** was prepared from 4.8 g (0.019 mol) of **7** and 7.05 g (0.038 mol) of iodoacetamide by the method used for **8** except that the reaction was complete at room temperature in 3 h without addition of further reagents. Following removal of the DMF the residue was treated with 25 mL of H_2O and 40 mL of $CHCl_3$. The chloroform layer was washed twice with 10-mL portions of H_2O and once with brine, concentrated to a 20-mL volume, and treated with excess 3.5 N ethereal HCl. Trituration of the gum with a few milliliters of acetone and dilution with 200 mL of Et_2O gave 6.1 g of crystalline **22**·HCl. Recrystallization from 250 mL of 4:1 CH_3CN–EtOH boiled down to a 150-mL volume gave 3.5 g of salt which intumesced at 233 °C. Concentration to a 50-mL volume gave 1.4 g more salt which intumesced at 227 °C.

Compound 24, (*exo,exo*)-2-(2-Thienyl)-8-azabicyclo-[3.2.1]octane-3-carboxylic Acid. A solution of 3.0 g (0.01 mol) of **7**·HCl in 40 mL of 4 N HCl was heated under reflux for 16 h and concentrated to a residue by warming in vacuo. Trituration with CH_3CN produced a crystalline product which was recrystallized by dissolving it in 10 mL of boiling EtOH, filtering, cooling, and adding 10 mL of Et_2O. Massive prisms separated (1.88 g) which melted at 209–212 °C with intumescence after being dried for 2 h at 55 °C (1 mm).

When an analysis was not satisfactory, the sample was recrystallized from concentrated ethanolic solution to give 1.35 g of prisms which melted at 189–190 °C with intumescence after being dried for 4 h at 100 °C (1 mm) and 22 h at 118 °C (1 mm). The NMR spectrum showed a weak methyl triplet indicating EtOH and the analytical values corresponded to $^1/_3$ mol of EtOH present.

Compound **25**, **ethyl (*exo,exo*)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was made from methyl ester **7** by hydrolysis and reesterification. A solution of 5.0 g (0.02 mol) of **7** in 100 mL of 2 N HCl was heated under reflux for 24 h and then concentrated to a residual solid by warming in vacuo. This solid in 50 mL of absolute EtOH was saturated with HCl gas and then heated under gentle reflux for 4 h with a continuing stream of HCl. Concentration of the solution by warming in vacuo and recrystallization of the residue furnished 4.15 g of **25**·HCl with a second crop of 0.4 g which melted 1 °C lower.

Compound **26**, **ethyl (*exo,exo*)-8-methyl-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was made from (±)-**6** by hydrolysis and reesterification. A solution of 25 g of (±)-**6** in 210 mL of 4 N HCl was heated on the steam bath for 20 h and then refluxed for 22 h. Concentration gave a residue which crystallized upon standing with 50 mL of acetone. The mixture was diluted with 50 mL of acetone and filtered to give 25.7 g (95%) of **(*exo,exo*)-8-methyl-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid hydrochloride.**

Esterification of 6.0 g (0.021 mol) of this salt was accomplished by the method used for **25**. The acid was slower in dissolving than in the preparation of **25**. When the product failed to crystallize as an HCl salt, it was converted to the free base which was distilled, giving 4.25 g of pure, oily **26**.

Compound **27**, **ethyl (*exo,exo*)-8-(1-pentyl)-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared by hydrolyzing 6.10 g (0.019 mol) of **10** with HCl and reesterifying with EtOH as for **25**. When the HCl salt of the product failed to crystallize, the free base was liberated with NH_4OH and distilled to give 5.23 g of pure **27**.

Compound 28, 1-Propyl (*exo,exo*)-8-Methyl-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate. A solution of 7.0 g (0.024 mol) of the acid produced from hydrolysis of (±)-**6** (see first paragraph in the preparation of **26**) in 37 mL of 2 N NaOH was concentrated to a residue in vacuo. The resulting sodium salt was suspended in 65 mL of hexamethylphosphorous triamide (HMPA), 16.6 g (0.098 mol) of 1-propyl iodide was added, and the mixture was stirred at room temperature for 40 h. Most of the HMPA was removed by distillation at a bath temperature of 150 °C using 1.5 mm of pressure. The residue was stirred with 150 mL of Et_2O, the mixture was filtered, and the filtrate was washed with six 50-mL portions of H_2O. Concentration of the filtrate and distillation of the residue gave 5.17 g of **28**.

Compound **29**, **1-pentyl (*exo,exo*)-8-methyl-2-(2-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared in a manner identical with that for **28** except that, instead of the product being distilled, it was dissolved in ether and treated with 1 equiv of hexamic acid. Two recrystallizations of the resulting crystalline salt from CH_3CN failed to give analytically pure material so the base was recovered and chromatographed on silica preparative plates using 3:97 *i*-$PrNH_2$–Et_2O. The pure material from the plates was distilled to give **29** (Table V).

Compound 30, (*exo,exo*)-1-[8-Methyl-2-(2-thienyl)-8-azabicyclo[3.2.1]octan-3-yl]ethanone. A stirred solution of 12.0 g (0.045 mol) of (±)-**6** in 100 mL of Et_2O at 5–10 °C was treated in 45 min with 21.5 mL (0.056 mol) of 2.6 M ethereal CH_3MgBr which had been diluted with 100 mL of Et_2O. The mixture was stirred for 1.5 h at 10–20 °C and poured into 50 mL of 2 N HCl and 50 g of ice. The layers were separated and the Et_2O layer was washed with 25 mL of 2 N HCl. Washing of the acid portions with Et_2O, followed by basification, afforded 11.3 g of oil which, upon dilution with 15 mL of pentane, precipitated 8.3 g of prisms.

Treatment of these prisms in 20 mL of MeOH with 19 g of sodium metabisulfite in 100 mL of H_2O and extraction of this mixture with seven 30-mL portions of CH_2Cl_2 gave 7.1 g of extracted oil. Hydrolysis of the aqueous solution with 25 g of added $NaHCO_3$ and 75 mL of CH_2Cl_2 at reflux for 5 h gave 1.04 g of crystalline solid which, even after preparative TLC and two recrystalizations from cyclohexane, softened at 95 °C and melted at 105–111 °C (impure **30**).

Preparative TLC of the 7.1 g of extracted oil (1:10:89 *i*-$PrNH_2$–Et_2O–pentane) gave 3.28 g of recovered (±)-**6** (27%) and 3.4 g of **30**. Recrystallization from 3.5 mL of cyclohexane (separation by centrifugation) gave 2.50 g of **30** base (Table V). **30**·HCl is also described in Table V.

Compound 31, Methyl (*exo,exo*)-8-Methyl-2-(3-thienyl)-8-azabicyclo[3.2.1]octane-3-carboxylate. This equatorial ester was formed by the addition of 3-thienylmagnesium bromide to ester (±)-**51**.[4] The Grignard reagent did not form in appreciable quantity when the reactants were assembled in the usual manner, and the Mg was activated by a small quantity of ethylene dibromide. A mixture of 18.4 g (0.76 g-atom) of Mg, 32.0 g (0.196 mol) of 3-bromothiophene, 3 mL of ethylene dibromide, and 50 mL of Et_2O was charged into an appropriate flask and the reaction was initiated with a crystal of I_2. When a vigorous reaction started, 100 mL of Et_2O was added and a solution of 76 g (0.40 mol) of ethylene dibromide in 50 mL of Et_2O was added dropwise over a period of 3.5 h to the refluxed mixture. The ethylene evolved entrained considerable Et_2O so it was necessary to replace it periodically in order to maintain a satisfactory reaction volume. When addition of the halide was complete, the mixture was refluxed for an additional hour. Titration of an aliquot by adding it to an excess of 0.1 N HCl and back-titrating with 0.1 N NaOH indicated that RMgBr formation was 77% complete.

The reaction mixture was then chilled to −20 °C and 10.0 g (0.055 mol) of ester ±-**51**[4] was added as in the standard method.[4] Workup gave 12.9 g of crude base which was distilled. The expected mixture of epimers boiled at 112–122 °C (0.5 mm): 9.6 g, 66%. Conversion of the mixture to the exo epimer **31** was then accomplished by treatment with 0.22 g of $NaOCH_3$ in 55 mL of

MeOH at reflux under N_2 for 1.5 h. Workup as for **13** gave 9.17 g of oily **31**. Conversion to the HCl salt gave only an amorphous product so the free base was liberated (7.7 g) and distilled, giving 6.9 g of **31**. NMR spectroscopy indicated that this product (OCH_3 peak at 3.40 ppm) contained 14% of the endo epimer with the OCH_3 peak at 3.70 ppm.

Compound **35**, **methyl (*exo,exo*)-8-(cyclopropylmethyl)-2-phenyl-8-azabicyclo[3.2.1]octane-3-carboxylate,** was prepared from its 3-endo epimer[4] by treating 4.5 g (0.0134 mol) of the latter (as its HCl salt) in 35 mL of MeOH with 1.0 g of $NaOCH_3$ and refluxing the mixture for 4.5 h. Workup as for **13** gave 3.8 g of oil which contained (by NMR) 15% of the unchanged 3-endo epimer. The endo epimer OCH_3 signal appeared at 3.6 and that of the exo epimer at 3.3 ppm. Chromatography of the sample on 15 preparative silica plates using 5:10:85 HCOOH–MeOH–$CHCl_3$ gave 2.76 g of pure **35** which formed a crystalline *p*-toluenesulfonate salt in EtOAc. One recrystallization gave the **35** salt described in Table V.

Compound **39**, **(*exo,exo*)-1-(8-methyl-2-phenyl-8-azabicyclo[3.2.1]octan-3-yl)ethanone,** was prepared in the same manner and on the same scale as **30** but using 2-phenyl ester **5**. The precipitate formed here upon Grignard addition was much heavier than that produced with (±)-**6**. The crude base crystallized and, upon recrystallization from hexane, gave 6.82 g of needles of **39** base, mp 95–97 °C. The HCl salt of this base was recrystallized twice to give 4.67 g of **39**·HCl.

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