Table III

	1	2	3
Solvent	EtOAc	EtOAc	EtOH–Et_2O
a, Å	7.735 (1)	8.060 (1)	11.662 (2)
b, Å	12.068 (1)	15.011 (1)	13.265 (3)
c, Å	21.484 (3)	18.611 (2)	13.048
β, deg	104.52 (1)	99.42 (1)	90.0
Sp gr	$P2_1/c$	$P2_1/c$	$P2_12_12$
d (measd), g/cm^3	1.181	1.166	1.195
d (calcd), g/cm^3	1.190	1.166	1.197[a]
Z	4	4	4
R value (final)	0.038	0.046	0.074

[a] As monohydrate.

and calculated structure factors is available from the author on request.

Acknowledgment. The author is grateful to Mrs. Phyllis Sackman for her very capable technical assistance, to the National Institutes of Health for financial support (CA-10104), to the Computing Center of this University for use of their facilities, and to Dr. Philip S. Portoghese for his interest.

Supplementary Material Available. Tables IV and V will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-1037.

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In Pursuit of Analgetic Agents. Hydro-1,3-ethanoindeno[2,1-*c*]pyridines and Homologs

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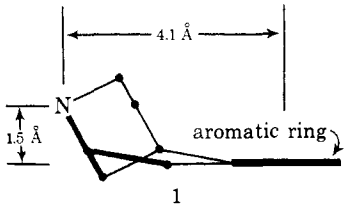
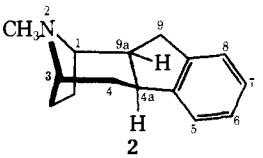
A study was made of the analgesic activity associated with a modified skeletal support for the nitrogen atom and the aromatic ring of the benzomorphans. The compounds involved were 1,2,3,4,4a,9a-hexahydro-9*H*-1,3-ethanoindeno[2,1-*c*]pyridines of general structure **2** with various substituents on N, C-9, and the aromatic ring. Also included were some "middle ring homologs" which belong to the chemical category of 1,3-ethanobenz[*g*]isoquinolines. These compounds showed activity in preventing the abdominal constriction response in mice induced by acetylcholine and phenyl-*p*-quinone. They were inactive in the D'Amour-Smith "tail flick" test. The three most promising compounds failed to block the intraarterial bradykinin-evoked pain response in the rat. Selected compounds, evaluated as local anesthetics, showed activity in the procaine-cocaine range. Removal of the ethano bridge present in these compounds had no significant effect on the level of activity observed in this series.

The benzomorphan class of analgesics is characterized by the presence of a basic nitrogen atom rather rigidly held about 1.5 Å above the plane of an aromatic ring and displaced about 4.1 Å from the center of that ring (see **1**). A new series of polycyclic bases, the recently described ethanoindeno[2,1-*c*]pyridines,[1] exemplified by structure **2**, has a nitrogen atom suspended about 1.8 Å above the plane of the aromatic ring and displaced about 4.4 Å from the center of this ring. It was therefore of considerable interest to determine the degree of analgesic activity associated with these modified dimensions and a modified supporting skeleton.



1



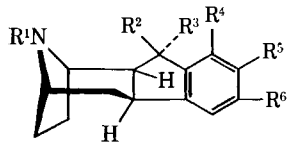
2

The present paper describes the preparation of a variety of substituted hydro-1,3-ethanoindeno[2,1-*c*]pyridines, some homologous compounds with the "center" ring enlarged, and a parallel series with the ethano bridge absent.† Structure-activity relationships have been investigated through measurement of prevention of the abdominal constriction response in mice induced by acetylcholine (ACh) and phenyl-*p*-quinone (PPQ). Also used were the D'Amour-Smith tests for narcotic analgesia and narcotic antagonism. Blockade of bradykinin-induced asymmetric motion was the most definitive test employed for nonnarcotic analgesia. Limited data are furnished on toxicity and local anesthetic activity. Biological activity is reported here for 11 indenopyridines described chemically in ref 1.

Chemistry. The general procedure for preparing hexahydro-1,3-ethanoindeno[2,1-*c*]pyridines[1] is shown in eq 1. The mixture of 2α and 2β esters represented by formula **3** was formed by Grignard 1,4 addition to an α,β-unsaturated ester precursor[3] and can be used without separation

† Phenindamine, an antihistaminic agent, is a 9-phenyltetrahydro-1*H*-indeno[2,1-*c*]pyridine. Augstein, *et al.*,[2] report studies on the antidepressant properties of a series of 9-phenylhexahydro-1*H*-indeno[2,1-*c*]pyridines and 5-phenylhexahydro-2*H*-indeno[1,2-*c*]pyridines.

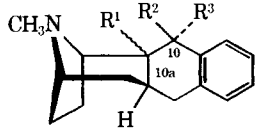
Table I



Compd[a]	R1	R2	R3	R4	R5	R6	Formula	Yield, %	Mp, °C	$[\alpha]^{25}D$, deg	Analyses
5	CH_3	Carbonyl		H	F	H	$C_{15}H_{16}FNO \cdot HCl$	70[g]	285[b-e]	+36.2[f]	C, H, Cl
6	CH_3	H	H	H	F	H	$C_{15}H_{18}FN \cdot HCl$	74[g]	286–287[d,e]	+83.4[f]	C, H, Cl
7[h]	CH_3	OH	H	H	F	H	$C_{15}H_{18}FNO \cdot HCl$	26[g]	268–270[b,d]	+68.0[f]	C, H, Cl
8[h]	CH_3	OAc	H	H	F	H	$C_{17}H_{20}FNO_2$	86[g]	128–129[i]	+59.3[j]	C, H, N
9	CH_3	Carbonyl		H	OCH_3	H	$C_{16}H_{19}NO_2$	29[g]	107–108.5[k,l]	−22.5[j]	C, H, N
10	CH_3	OH	H	H	OCH_3	H	$C_{16}H_{21}NO_2 \cdot HCl$	20[g]	269–271[b,d,l,m,o]	+26.9[f]	C, H, Cl
11	CH_3	H	H	H	OCH_3	H	$C_{16}H_{21}NO \cdot C_7H_8O_3S$	70[g]	275[b,m,n]	+49.2[f]	C, H, S
12	CH_3	Carbonyl		H	H	OCH_3	$C_{16}H_{19}NO_2 \cdot HCl$	43[g]	213–215[b,d,h,o]	+77.4[f]	C, H, Cl
13	CH_3	H	H	H	H	OCH_3	$C_{16}H_{21}NO \cdot H_2SO_4$	74	195–197[b,e,o,q,r]	+93.7[f]	C, H, S
14	CH_3	H	H	H	H	OH	$C_{15}H_{19}NO \cdot HBr$	81	298–299[o,s]	+94.9[f]	C, H, Br
15	CH_3	Carbonyl		OCH_3	H	H	$C_{16}H_{19}NO_2$	13	143–145[t,v]	−15.8[j]	C, H, N
16	CH_3	H	H	OCH_3	H	H	$C_{16}H_{21}NO \cdot C_7H_8O_3S$	86[g]	147.5–151[h,l,m]	+40.2[f]	C, H, S
17	EtOCO	H	H	H	H	H	$C_{17}H_{21}NO_2$	77.5	152–160[t]	+126[j]	C, H, N
18	H	H	H	H	H	H	$C_{14}H_{17}N \cdot HCl$	80	303[b,d,e]	+88[f]	C, H, Cl
19	CH_2CH_2CHCO-	H	H	H	H	H	Used crude				
20	$CH_2CH_2CHCH_2-$	H	H	H	H	H	$C_{18}H_{23}N \cdot HCl$	95	239–240[d,h]	+85.6[f]	C, H, Cl
21	$C_6H_5CH_2$	H	H	H	H	H	$C_{21}H_{23}N \cdot C_7H_8O_3S$		217–219[h,n,u]	+98.0[v]	C, H, N
22	$HOCH_2CH_2$	H	H	H	H	H	$C_{16}H_{21}NO \cdot HCl$	69[d]	230–232[g]	+81.4[f]	C, H, N

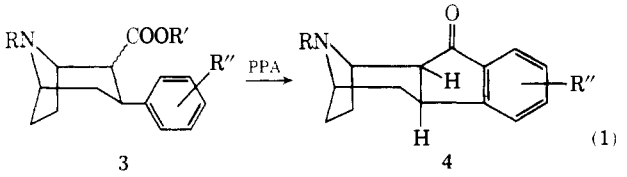
[a]The absolute configurations at carbons 1, 3, 4a, and 9a are *R*, *S*, *S*, and *S*, respectively. [b]Decomposition. [c]Massive prisms. [d]HCl salt. [e]From CH_3CN. [f]In H_2O. [g]Yield of base. [h]The absolute configuration at C-9 is *R*. [i]From pentane. [j]In $CHCl_3$. [k]From hexane. [l]Needles. [m]From absolute EtOH. [n]*p*-Toluenesulfonate salt. [o]Evacuated capillary. [p]From THF. [q]Plates. [r]Sulfate salt. [s]Hydrobromide. [t]Bp at 0.7 mm. [u]After melting at 206–207° and resolidifying. [v]In EtOH.

Table II



Compd	R1	R2	R3	Formula	Abs config[a] at C-10	Abs config[a] at C-10a	Yield, %[b]	Mp, °C	$[\alpha]^{25}D$, deg	Analyses
24	ξ	Oxygen		$C_{16}H_{19}NO$		*R,S*	63	239–241[c,d]	−11.7[e]	C, H, Cl
25	α-H	OH	H	$C_{16}H_{21}NO$	*R*	*S*	7	149–151[c,f]	−39.5[g]	C, H, N
26	α-H	H	H	$C_{16}H_{21}N \cdot HCl$		*S*	6	294–295[h-j]	+44.1[e]	C, H, N
27	β-H	H	OH	$C_{16}H_{21}NO \cdot HCl$	*S*	*R*	37	328[c,j,k]	−37.6[e]	C, H, Cl
28	β-H	H	H	$C_{16}H_{21}N \cdot HCl$		*R*	6	302–303[c,j,l]	+42.0[e]	C, H, Cl

[a]The absolute configurations at carbons 1, 3, and 4a are *R*, *S*, and *S*, respectively. [b]Yield of free base. [c]Prisms. [d]From acetone. [e]1% in H_2O. [f]From hexane. [g]1% in $CHCl_3$. [h]Needles. [i]From acetone. [j]Decomposition. [k]From EtOH. [l]From MeOH.



3 4 (1)

in the ring closure process. The basic chemistry of this cyclization is being reported in a companion paper.[1]

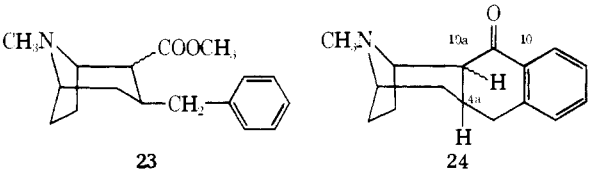
The fluoro compounds of Table I (no. 5–8) were prepared in the standard manner.[1] Attempted ring closure at the usual 150° failed where the aromatic ring carried a 4-methoxy group, apparently owing to ether cleavage. Hydrolysis to the corresponding acid 3 (R = CH_3; R′ = H; R″ = 4-OCH_3) gave a compound which could be cyclized by polyphosphoric acid (PPA) at 100° with an optimum time of 16 hr but even then the yield of 9 (Table I) was only 29%. HF failed to effect this cyclization.

This same hydrolysis-ring closure procedure was used where a 3-methoxy group was present (3, R = R′ = CH_3; R″ = 3-OCH_3) but here the yield of cyclized material was 56%. Ring closure occurred both para and ortho to the methoxyl, producing 43% of 4 (R = CH_3; R″ = 6-OCH_3) and 13% of 4 (R = CH_3; R″ = 8-OCH_3) (compounds 12 and 15 of Table I).

Whereas ketones of type 4 were normally reduced by diborane to form mixtures of 9-alcohols and 9-methylene derivatives,[1] electron donation by the 6- and 8-methoxyl groups activated the 9 position to such an extent that only the 9-methylene derivatives were formed (13 and 16). There was no assistance from a 7-methoxyl group in this reduction and a normal mixture of 9β-alcohol 10 and 9-methylene derivative 11 was formed. The 9β-alcohol showed expected intramolecular H bonding. Phenolic amine 14 resulted from treatment of ether 13 with HBr.

Ethyl chlorocarbonate demethylated amine 2 to form urethane 17 which was hydrolyzed by hot 2 *N* HCl to give the secondary amine 18. Cyclopropanecarboxylic acid chloride converted 18 to amide 19 which was reduced ($LiAlH_4$) to the *N*-cyclopropylmethyl derivative 20. Treatment of amine 18 with benzoyl chloride followed by $LiAlH_4$ produced 21. Ethylenebromohydrin reacted with 18 to form 22.

When isomer mixture 23, prepared from (−)-anhydroecgonine and homologous with 3, was cyclized, it formed what was probably a mixture of cis and trans ketones 24 (Table II). These isomers were not separable by glpc but the substantial amounts of both cis- and trans-fused products formed by reduction as described below indicated that both isomers were present.



23 24

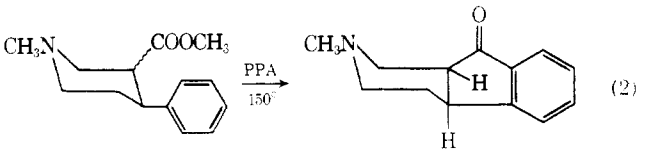
Reduction of this material with diborane produced a mixture of two 9-methylene derivatives and two alcohols. Alcohol 25 had cis-fused rings and the 9-OH β since it showed intramolecular H bonding with the nitrogen. The corresponding *cis*-9-methylene derivative 26 was recognizable in that it failed to react with EtI at room temperature owing to the axial orientation of the substituent at "carbon 2" of the tropane moiety. The *trans*-9-methylene derivative 28 was expected to show no hindrance to quaternary formation and indeed it reacted readily with EtI.

The structural assignments for this pair of cis–trans isomers (26 and 28) were also supported by nmr data. In the spectrum of trans isomer 28 the four benzylic hydrogens were superimposed. In the spectrum of cis isomer 26 the β C-10 hydrogen was deshielded by the nitrogen atom and appeared at 3.28 ppm. The other three benzylic hydrogens in 26 appeared at 2.95, 2.62, and 2.35 ppm.

The other alcohol (27) from the mixture reacted with EtI, confirming a trans ring fusion, but the configuration of the hydroxyl group is problematical. Nmr data favor the α form since the latter would normally eclipse a methylene group of the ethano moiety. Relief of this interaction should produce a distortion that would bring the dihedral angle between the 9β-H and the 9aβ-H to about 25°, a value consonant with the observed J = 8–9 Hz. As expected, the ir spectrum of this alcohol showed no intramolecular H bonding.

All of the compounds described up to this point were prepared from "natural" (−)-anhydroecgonine methyl ester and thus have the 1*R*,3*S*,4a*S*,9a*S* (Table I) or the 1*R*,3*S*,4a*S* (Table II) configurations. In order to determine the role of chirality in the biological activity of this series, two pairs of optical antipodes described chemically in ref 1 are evaluated in the Biology section below.

Some measure of the effect of molecular rigidity on the antiwrithing activity observed was sought by preparing a group of indeno[2,1-*c*]pyridines in which the ethano bridge was absent (see Table III). The required esters 29 have been reported by Plati, *et al.*,[4] and their configurations established by Clarke, *et al.*[3] Both esters afforded the same cis-fused product 30[4] according to eq 2. $NaBH_4$ reduced the carbonyl of 30 with formation of only one of the two possible epimeric alcohols. It was assigned the β configuration (31) since it exhibited intramolecular hydrogen bonding. The 9-methylene compound in this series, 33, was obtained *via* desulfurization of an intermediate thioketal 32. The cis nature of the ring fusion in 33 was established by comparison with an authentic sample prepared by another route.‡



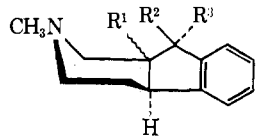
29 30 (2)

The 9,9-dimethyl derivatives in this same series (34 and 35, Table III) were obtained starting from esters 29 mentioned above. Treatment of 29 (trans ester) with CH_3MgCl gave tertiary alcohol 36 (Table IV) which lost water at 100° in the presence of H_2SO_4-HOAc (15 min) to give almost entirely the 3-(1-methylvinyl) derivative 39. After 4 hr the yield of 39 was reduced to 30% (isolated) since concomitant isomerization produced 48% of the 3-isopropylidene derivative 38. Treatment of 29 (cis ester) with CH_3MgCl gave tertiary alcohol 37 which was dehydrated by the same means in 5 min to give almost entirely the 3-isopropylidene derivative 38. Heating the mixture for 3 hr caused isomerization as above but "from the opposite direction." The equilibrium ratio was not established owing to the low yields of isolated material.

Cyclization of the 3-(1-methylvinyl) olefin 39 with PPA at 150° then gave the desired trans 9,9-dimethylated product 34 (77%) with no evidence for the presence of the cis isomer. This trans assignment is based on knowledge of the configuration of the starting material and the unlikelihood that the thermodynamically more stable equatorial substituent on C-2 of the intermediate 40 would completely assume the less stable axial configuration prior to

‡ W. F. Michne, A. J. Gambino, and R. L. Clarke, unpublished results.

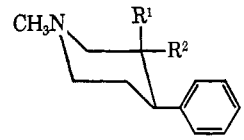
Table III



Compd[a]	R[1]	R[2]	R[3]	Formula	Yield, %[b]	Mp, °C	Analyses
30	α-H	Oxygen		$C_{13}H_{15}NO$	60	66–67[c]	Known[k]
31	α-H	OH	H	$C_{13}H_{17}NO$	60	150–151[d-f]	C, H, N
32	α-H	$-SCH_2CH_2S-$		$C_{15}H_{19}NS_2$	46	115–118	Crude
33	α-H	H	H	$C_{13}H_{17}N \cdot HCl$	58	198–199[e,h]	C, H, Cl
34	β-H	CH_3	CH_3	$C_{15}H_{21}N \cdot HCl$	14	323–324[e,i,j]	C, H, Cl
35	α-H	CH_3	CH_3	$C_{15}H_{21}N \cdot HCl$	14	188–190[d,f]	C, H, Cl

[a]All of the compounds are racemates. [b]Yield of free base. [c]From pentane. [d]Needles. [e]Decomposition. [f]From EtOAc. [g]Prisms. [h]From acetone. [i]Rods. [j]From CH_3CN. [k]See ref 2.

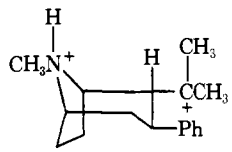
Table IV



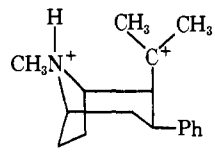
Compd[a]	R[1]	R[2]	Formula	Yield, %[b]	Mp, °C	Analyses
36	H	$-C(CH_3)_2OH$	$C_{15}H_{23}NO \cdot HCl$	52	248–249[c,d]	C, H, Cl
37	$-C(CH_3)_2OH$	H	$C_{15}H_{23}NO \cdot HCl$	93	235–236[d,e]	C, H, Cl
38	$=C(CH_3)_2$		$(C_{15}H_{21}N)_2 \cdot C_{10}H_8O_6S_2$	48	235–237[d,e]	C, H, Cl
39	H	$-C(CH_3)=CH_2$	$C_{15}H_{21}N \cdot HCl$	30	232–233[e,f]	C, H, Cl

[a]All compounds are racemates. [b]Yield of free base. [c]Decomposition. [d]From CH_3CN. [e]Prisms. [f]From acetone.

reaction. Further, Dreiding models indicate that of the two possible intermediate carbonium ions **40** and **41**, the equatorial one (**40**) is sterically more favorably disposed for cyclization.



40



41

Since the 3-isopropylidene olefin **38** might logically cyclize also to give trans-fused product **34** through the intermediacy of **40** (axial protonation of the double bond of **38** on carbon 2), we turned to the *cis*-carbinol **37** as a possible source of the cis-fused product. Here at least the initially formed carbonium ion **41** would have the desired 2,3-cis configuration. In actuality, equal amounts (11%) of the cis and trans products **35** and **34** were isolated from this reaction mixture in an inefficient separation procedure.

Biological Studies. The ethanoindenopyridines described here and in ref 1 were screened for analgesic activity by measuring the prevention of the abdominal constriction response in mice. Acetylcholine (ACh)[6] and phenyl-*p*-benzoquinone (PPQ)[7] served as the constricting agents. The compounds were further evaluated in the D'Amour–Smith "tail flick" test both for narcotic type analgesia and narcotic antagonism.[8]

The results of all these tests are summarized in Tables V and VI. The criteria for interest were activity both subcutaneously and orally in the ACh and PPQ tests at ≤40 mg/kg and a negative D'Amour–Smith narcotic type response. All of the compounds reported showed negative D'Amour–Smith "tail flick" responses at the maximum doses recorded in the tables. Narcotic antagonism was likewise absent except for compound **39** which showed a questionable antagonism toward phenazocine (ED_{50} = 56 mg/kg) with a maximum blocking effect of 69%.

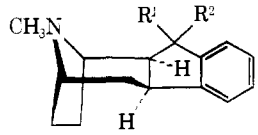
In the tests for prevention of the abdominal constriction response, many compounds were eliminated from consideration owing to toxic manifestations. The Remarks column of the tables contains limited data of this nature. In the group studied, compounds B, C, and I showed the most promise as analgesics. For comparison with pentazocine, see the third from last entry of Table VI.

As a further measure of authentic analgesic activity, B, C, and I were evaluated for their ability to block the intraarterial bradykinin-evoked pain response in the rat.[9] Compound B was inactive at 150 mg/kg sc and was lethal at 300 mg/kg. Its enantiomer, I, showed some activity at 50–75 mg/kg sc accompanied by tremors and ataxia. Deaths occurred at 100 mg. Compound C was weakly active at 100–150 mg/kg sc with tremors and severe ataxia above 100 mg. In contrast, pentazocine showed an ED_{50} of 2.6 (1.7–3.3) mg/kg sc.

Perhaps the prevention of the abdominal constrictive response effected by the presently reported compounds is related to the local anesthetic activity which they possess. Note the substantial antiwrithing activities of cocaine and procaine (local anesthetics) which are recorded at the end of Table VI. The local anesthetic action of seven of these compounds was evaluated in parallel with cocaine by means of an intradermal anesthetic test in guinea pigs.[10] In the following compilation the activity level of cocaine has been set at 1.0: cocaine, 1.0; A, 0.2; B, 1.0; C, 0.3; E, 0.3; I, 0.3; J, 0.3; **22**, 1.0.

It is of interest that the analgesic activity of pentazocine and cyclazocine resides in one optical antipode; the other is essentially inactive.[7] In the present series, where "classical" analgesia was not substantiated by the tests used, two pairs of optical antipodes (B *vs.* I and C *vs.* J) exhibited no appreciable differences in their abilities to prevent abdominal constriction.

Table V. Biological Activity of Ethanoindeno[2,1-c]pyridines in Ref 1



Compd	Prevention of abdominal constriction response (mice) ACh ED_{50}[a] sc	ACh ED_{50}[a] po	PPQ ED_{50}[a] sc	PPQ ED_{50}[a] po	D'Amour–Smith highest dose tested rats, sc,[a] inact.	Remarks: numbers[a] R = rats; M = mice
A[b]	18 (15–22)[c]	>40			120	Rigid, ataxic, 90 sc, R
B[d]	4.4 (3.5–5.5)	7 (4.2–12)	14 (5.5–25)	42 (32–57)	120	LD_{50} 15 iv,[e] 101 po,[e] M
C[f]	5.0 (2.8–7.3)	7.8 (5.3–11)	8.4 (5.9–11)	25 (22–33)	10	LD_{50} 36 iv,[e] 292 sc,[e] M
D[g]	2 (1.6–2.6)				30	6/6 dead, 80 sc, R
E[h]	28 (18–39)	>50				
F[i]	>0.8				0.94	LD_{50} 2.5 sc,[e] M
G[j]	1.8 (1.1–3.0)	2.6 (1.4–3.9)	15 (12–19)	51 (36–84)	120	Convul 10 sc, R
H[k]	11 (8.2–15)	29 (21–40)	18 (10–25)	85 (74–111)	120	LD_{50} 46 iv,[e] M
I[l]	4.6 (3.1–7.1)	4.2 (2.7–6.1)	19 (12–15)	23 (10–38)	120	LD_{50} 27 iv,[e] 152 po,[e] M
J[m]	10 (6.4–15)	11 (8.1–15)	12 (7.3–17)	40 (18–99)	120	LD_{50} 28 iv,[e] 93 sc,[e] M
K[n]	>30				120	

[a] mg/kg of free base. [b] $R^1 + R^2 = 0$. [c] Confidence limits calculated according to C. I. Bliss, "The Statistics of Bioassay," Academic Press, New York, N. Y., 1952. [d] $R^1 = R^2 = H$. [e] 7-Day test. [f] $R^1 = OH$; $R^2 = H$. [g] $R^1 = OAc$; $R^2 = H$. [h] $R^1 = H$; $R^2 = OH$. [i] $R^1 = R^2 = H$; $\Delta^{4a,9a}$. [j] $R^1 = R^2 = H$; $4\alpha\beta$, $9\alpha\beta$. [k] Enantiomer of A. [l] Enantiomer of B. [m] Enantiomer of C. [n] Enantiomer of E.

Conclusions

The present study was initiated to test the postulate that simple suspension of a nitrogen atom in a particular spatial relationship to an aromatic ring without regard to supporting skeletal characteristics would produce an analgesic agent. It did not prove valid in this case. The 1,3-ethanoindeno[2,1-c]pyridines reported here showed activity in preventing the abdominal constriction response in mice but this was not an indication of analgesic activity.

Experimental Section

All melting points were measured in capillary tubes and are uncorrected. Analytical results for indicated elements are within ±0.4% of the theoretical values. Uv spectra were measured in EtOH on a Cary Model 15 spectrophotometer. Nmr data on all compounds were consistent with assigned structures. They were recorded on a Varian HA-100 spectrophotometer. Ir spectral studies on hydrogen bonding were done using a Beckmann IR-7 spectrophotometer. Preparative plate chromatography was done with Brinkmann PF_{254} silica gel in 1-1.5 mm thickness on 20 × 40 cm plates.

The compounds described by number below are described physically in Tables I-IV.

Compound 5 was prepared by the method of Daum, *et al.*,[1] for **2a** in that reference. The required methyl 3β-(*p*-fluorophenyl)-1α*H*,5α*H*-tropane-2α- and -2β-carboxylates (mixture of isomers at C-2 and derived from "natural" (−)-anhydroecgonine methyl ester) are described by Clarke, *et al.*[3] Reduction of compound **5** with diborane in the manner described for the reduction of **2a** in ref 1 and distillation of the crude mixture gave the free base of **6** of Table I: bp 125–130° (0.7 mm); mp 51–54.5°. Its HCl salt is compound **6**. A fraction boiling at 130–147° (0.7 mm) afforded the free base of **7**, mp 114–115° from Et_2O.

Compound 8 was prepared from **7** and Ac_2O-pyridine.

Compound 9 required two stages in its preparation. Hydrolysis of the methoxy ester **3** (R = R′ = CH_3; R″ = 4-OCH_3)[3] by 21-hr reflux with 6 equiv of 2 *N* HCl followed by solvent removal gave a crystalline acid hydrochloride (61–72% yield). This acid salt was heated with PPA (20 g/g of salt) on the stream bath for 4 hr (caution: foaming) and worked up in the usual manner.[1] The crude product, which crystallized (29%), was dissolved in hot hexane, decolorized with Darco G-60, and precipitated by concentration and cooling: mp 103.5–108.5°. Material of this purity was used in the following reduction experiment. A sample was purified by preparative plate chromatography using two passes of 3:97 *i*-$PrNH_2$-Et_2O.

Reduction of compound **9** with diborane as above gave a crude mixture which was chromatographed on silica gel (40 g/g of compound) that had been treated with *i*-$PrNH_2$ (1 ml/4 g) prior to packing. Elution with 1:1 Et_2O-pentane gave the base of compound **11** as *large* plates from Et_2O. The base of compound **10** followed immediately from the column (same eluting solvent). A 0.005 *M* solution of **10** in CCl_4 showed a broad ir absorption band at 3160 cm^{-1} characteristic of intramolecular H bonding.

Compound 12 was prepared using the same two-step sequence as used for **9** above. The crude product was chromatographed on a silica gel column (40 g/g of oil) using Et_2O-pentane-*i*-$PrNH_2$ (79:20:1) for elution. A mixture of 6- and 8-methoxy ketones was obtained with no separation. This mixture was chromatographed on 20 × 40 cm preparative silica plates (0.25 g per plate) using three solvent passes of *i*-$PrNH_2$-Et_2O (3:97). The lead band afforded the free base of **12**: mp 92.5–94.5° (needles from hexane); uv max (95% EtOH) 224.5 nm (ε 14,000), 270 (14,300), 289 (12,000), and 296 (11,800).

Compound 15 was obtained as a trailing band on these plates.

Reduction of compound **12** with diborane as above gave **13** as the sole product isolated (crude product showed single tlc spot; silica gel, 3:97 Et_2O-*i*-$PrNH_2$).

Compound 14. When the sulfate salt **13** was heated under reflux for 2.25 hr with 48% aqueous HBr (5 ml/g) and the solution cooled and brought to pH 8 with concentrated NH_4OH, the HBr salt **14** of the corresponding phenol precipitated directly.

Reduction of compound **15** with diborane as above gave the 9-methylene compound **16** following chromatography on silica gel (80 g/g of product) using Et_2O-pentane-*i*-$PrNH_2$ (70:29:1) for elution. The salt **16** described in Table I formed massive prisms from H_2O, mp 133–135°, apparently a different polymorphic form from that in the table.

Compound 17 resulted from warming a mixture of 0.1 mol of (1*R*,3*S*,4a*S*,9a*S*)-1,2,3,4,4a,9a-hexahydro-2-methyl-9*H*-1,3-ethanoindeno[2,1-c]pyridine (**2c** of ref 1) and 0.2 mol of EtOCOCl on the steam bath until evolution of methyl chloride subsided. A second 0.2 mol of EtOCOCl was added and the mixture was heated under reflux for 4 hr. The cooled mixture was diluted with Et_2O, washed with 2 *N* HCl, concentrated, and distilled to give **17** of Table I, an oil with $n^{25}D$ 1.5491 which crystallized and melted at 88–90° (pentane).

Compound 18 was prepared by heating urethane **17** with 6 *N* HCl (20 ml/g) under reflux for 48 hr. Since the mixture was still heterogeneous, *n*-PrOH (8 ml/g) was added and reflux continued for 24 hr. Et_2O was added and the product extracted with 2 *N* HCl. Starting material recovered from the Et_2O was reprocessed. Concentration of the total acidic extracts afforded salt **18**.

Compound 20 was prepared in a two-step sequence. Cyclopropanecarboxylic acid chloride (5.25 g, 0.050 mol) was added drop-

Table VI. Biological Activity of Compounds of Tables I–IV

Compd	Prevention of abdominal constriction response (mice) ACh ED_{50}[a] sc	ACh ED_{50}[a] po	PPQ ED_{50}[a] sc	PPQ ED_{50}[a] po	D'Amour–Smith highest dose tested rats, sc,[a] inact.	Remarks: numbers[a] R = rats; M = mice
5	11 (9.1–17)[b]	13 (5.6–22)	20	80	120	1/6 dead 80 sc, R
6	3.6 (2.1–4.9)	9	44	25	120	1/6 dead 120 sc, R
7	~4[c]	~4[c]			60	5/6 dead 120 sc, R
8	5.4 (4.3–8.1)		30 (8.9–97)	>50	120	Convul 80 sc, R
11	~15[c]				60 ip	4/6 dead 120 ip, R
12	18 (13–29)	50 (27–74)	29 (17–54)	>100	60	1/6 dead 120 sc, R
13	~15[c]				120	LD_{50} 42 iv,[d] M
14	28 (22–39)				60	LD_{50} 36 iv,[d] M
15	33 (21–47)				120	
16	6.1 (4.6–8.1)		>50		120	Slight mydriasis 75 sc, M
17	>75				120 ip	
18	5 (3.3–7.7)	8 (5.2–13)	17 (12–29)	>50	120	5/15 dead 200 po, M
20	10 (8.3–14)	14 (11–17)	16 (12–25)	59	120	1/6 dead 120, sc R
21	>100				120 ip	1/6 dead 80 ip, R
22	6.3 (4.9–8.3)		~100[c]		120	Sedation 100 sc, M
24	5 (4.2–6.4)				60	5/6 dead 80 sc, R
25	4.7 (3.4–6.2)				120	2/6 dead 80 sc, R
26	3.1 (2.4–4.0)	6.9 (4.3–10)	8.8 (6.2–13)		120	2/6 dead 80 sc, R
27	9.0 (6.8–12)		23 (14–32)	46 (33–65)	120	Sedation 50 po, M
28	1.6 (0.6–2.6)				30	10/15 dead 75 sc, M
31	13 (9.7–18)	10 (6.3–16)	21 (15–18)	>100	120	Sedation 200 po, M
33	11 (8.0–14)	12 (7.6–16)	8.4 (5.9–26)	~75[c]	120	Tremors 80 sc, R
34	3.7 (1.8–17)		9.8 (6.6–15)		60	3/6 dead 80 sc, R
35	2.8 (2.1–3.8)				30	2/15 dead 75 sc, M
36	7.9 (4.4–14)		49 (30–71)		120	Tremors 120 sc, R
37	3.4 (2.4–4.3)	3.7 (2.2–5.6)	4.7 (3.4–7.2)	36 (21–28)	120	Sedation 100 sc, M
38	0.76 (0.43–1.2)				30 ip	3/6 dead 120 ip, R
39	2.3 (1.3–3.7)		8.9 (6.9–12)		120	Convul 100 sc, M
Pentazocine	2.2 (1.7–2.7)	51 (40–65)	2.3 (1.2–4.6)	Inact.		
Cocaine	3.8 (2.7–4.9)		24 (19–32)			
Procaine	35[e]					

[a] mg/kg of free base. [b] Confidence limits calculated according to C. I. Bliss, "The Statistics of Bioassay," Academic Press, New York, N. Y., 1952. [c] Nonlinear assay. [d] 7-Day test. [e] Reference 6.

wise to 10.0 g (0.050 mol) of **18** in 100 ml of $CHCl_3$ containing 5.1 g (0.050 mol) of Et_3N. The mixture was heated under reflux for 15 min, cooled, washed with 2 *N* NaOH, 2 *N* HCl, and brine, and dried (Na_2SO_4). Concentration afforded crude amide **19** which was dissolved in 100 ml of THF and added to 5 g of $LiAlH_4$ in 400 ml of THF. The mixture was heated under reflux for 5 hr, quenched with 10 ml of H_2O, and filtered. Concentration gave 11.5 g of the crude *N*-cyclopropylmethyl base of **20**.

Compound 21 was prepared from **18** in the manner for **20** using benzoyl chloride and $LiAlH_4$.

Compound 22 resulted when a mixture of 9.63 g (0.043 mol) of **18**, 6.96 g (0.082 mol) of $NaHCO_3$, 7.1 g (0.047 mol) of ethylene bromohydrin, and 50 ml MeOH was stirred at room temperature for 96 hr. Et_2O was added, the mixture was filtered, and the filtrate was washed (brine), dried (Na_2SO_4), and concentrated to give 7.2 g of crude **22**: M^+ 243.

Methyl (1*R*,2*RS*,3*S*,5*S*)-3β-Benzyl-1α*H*,5α*H*-tropane-2α- and -2β-carboxylate (23). Benzylmagnesium chloride was prepared from 112 g (0.74 mol) of benzyl chloride and 26.8 g (1.1 g-atoms) of Mg turnings in 750 ml of Et_2O and chilled to −20°. A solution of 72.0 g (0.40 mol) of (−)-anhydroecgonine methyl ester in 375 ml of Et_2O was added with stirring at −20 to −25° in 30 min and the mixture was stirred at this temperature (with difficulty owing to gum formation) for 15 min. Ice and H_2O (about 200 ml) were added followed by 2 *N* HCl to acidity and dissolution of all solid. The layers were separated and the H_2O layer was washed with Et_2O. The H_2O layer was made basic with concentrated NH_4OH and extracted four times with Et_2O. The dried (Na_2SO_4) extracts were concentrated and the residual oil (86.7 g) was distilled, the product being collected at 143–152° (0.8–0.6 mm), 36.7 g (34%), $n^{25}D$ 1.5317.

In a similar run the analytical sample was taken as a center cut from the distillation, $n^{25}D$ 1.5326. *Anal.* ($C_{17}H_{23}NO_2$) C, H, N.

Compound 24. PPA (58 ml) was heated to 100° and 8.4 g (0.031 mol) of isomer mixture **23** was added. The mixture was heated at 150° for 5 hr and worked up in the standard manner. Distillation of the oily product gave 4.5 g of amber oil: bp 136–146° (0.15–0.2 mm), $n^{25}D$ 1.5744. Glpc (160° isothermal on OV-17 on Gas Chrom Q) showed 95% of the material as a single peak. The HCl salt is compound **24** of Table II.

Reduction of Compound 24 with Diborane. A solution of 30.0 g (0.125 mol) of **24** in 500 ml of THF was added dropwise with stirring to 750 ml of 1 *M* diborane in THF under N_2 at 5–10° in 20 min. The solution was refluxed for 16 hr, quenched with 60 ml of H_2O, treated with 300 ml of 2 *N* NaOH, and refluxed for 2 hr. The THF was boiled out on the steam bath and the residual mixture was saturated with NaCl and extracted three times with Et_2O. Concentration gave a pasty residue which was triturated twice with pentane (150 ml). The solid, 17.7 g of mp 140–145°, was recrystallized from CH_3CN to give 11.2 g of prisms, mp 166–168° (possible transformation at 128–132°), of 1,2,3,4,4a,5,10,10a-octahydro-2-methyl-1,3-ethanobenz[*g*]isoquinolin-10-ol. In 0.005 *M* solution (CCl_4), it showed only nonbonded OH (3600 cm^{-1}). Its HCl salt is compound **27** of Table II.

The pentane triturate above, from which **27** was separated, contained 11.4 g of an oily mixture of products. Column chromatography on 450 g of silica gel using Et_2O–pentane mixtures for elution failed to give separation. The 7.9 g of oil recovered from the column was chromatographed on 24 preparative silica plates (20 × 40 cm) (3:97 *i*-$PrNH_2$–Et_2O) to give three major products.

The least polar band afforded 1.6 g of crystalline benz[*g*]isoquinoline (**26**), mp 83–85°. Its HCl salt is compound **26** of Table II.

The band of intermediate polarity furnished 2.1 g of crystalline benz[*g*]isoquinolin-10-ol (**25**), mp 138–145°. One crystallization from hexane gave compound **25** of Table II. In 0.005 *M* solution (CCl_4) it showed intramolecular H bonding (3205 cm^{-1}).

The most polar band (2.1 g of oil) had to be rechromatographed on eight preparative plates using three passes of the same solvent system. Thus was obtained 1.8 g of oily benz[*g*]isoquinoline (**28**)

which formed a crystalline HCl salt, compound 28 of Table II.

Rates of Quaternization of 26 and 28. The cis base **26** (60 mg) in 0.7 ml of acetone was treated with 0.17 ml of EtI at 24°. After 1 hr the precipitated quaternary salt was collected, 1.0 mg, 1% of theory.

The trans base **28** (88 mg) in 1 ml of acetone was treated with 0.2 ml of EtI at 24°. After 1 hr the precipitated quaternary salt was collected, 61 mg, 41% yield.

Compound 30. An approximately 1:1 mixture of *cis*- and *trans*-methyl (±)-1-methyl-4-phenyl-3-piperidinecarboxylate (68.3 g, 0.29 mol), prepared by the method of Plati, *et al.*,[4] was mixed thoroughly with 500 ml of PPA at 100° and the temperature was raised to 150° for 5 hr. The mixture was made strongly alkaline with concentrated NH_4OH and the product extracted with Et_2O. Concentration gave a solid which was recrystallized to give **30** of Table III, reported by Plati *via* another route.

Compound 31. A stirred solution of 14.7 g (0.073 mol) of ketone **30** in 75 ml of absolute EtOH was treated with 2.8 g (0.073 mol) of solid $NaBH_4$ portionwise and the mixture was allowed to stand for 16 hr. HCl (30 ml, 2 *N*) was added, and the EtOH was removed by warming *in vacuo*. Concentrated NH_4OH was added and the product was extracted by three portions of $CHCl_3$. The dried (Na_2SO_4) extracts were concentrated to give 15.7 g of beige solid, mp 135–137°. Two recrystallizations from EtOAc gave **31** of Table III. In 0.005 *M* solution (CCl_4) it showed only intramolecular H bonding (3320 cm^{-1}).

Compound 32. A solution of 21.3 g (0.090 mol) of ketone **30** hydrochloride salt, 47 ml of ethanedithiol, and 20 ml of $BF_3 \cdot Et_2O$ in 200 ml of HOAc stood for 66 hr. A crystalline precipitate formed which was apparently an impure BF_3 salt of the desired thioketal (Calcd for $C_{15}H_{19}NS_2$: F, 16.5. Found: F, 18.3). Et_2O (500 ml) was added to complete precipitation and the precipitate was treated with concentrated NH_4OH. Et_2O extraction gave **32**.

Compound 33 by Desulfurization of 32. Two tablespoons of W-2 Raney nickel was suspended in 190 ml of 95% EtOH and the mixture was saturated with H_2 under 3.5 kg/cm^2 pressure. (When the catalyst was not well saturated with H_2, a product containing an additional double bond was formed.) Then 7.1 g (0.026 mol) of crude thioketal **32** was added and the mixture was refluxed for 72 hr. Glpc (OV-17 on Gas Chrom Q at 150° until reduced products came off, then to 250°) showed a major amount of thioketal was still present so the catalyst was replaced by a fresh batch (prepared as above) and reflux was continued for 16 hr. No thioketal remained. Removal of catalyst and solvent gave an oil (4.0 g) which formed a crystalline HCl salt, **33**. A mixture melting point with **33** prepared by another route‡ showed no depression and their ir and nmr spectra were identical.

Compound 36. A solution of 29.4 g (0.13 mol) of *trans*-methyl (±)-1-methyl-4-phenyl-3-piperidinecarboxylate[3] in 60 ml of THF was added in 15 min to 127 ml (0.38 mol) of 3 *M* CH_3MgCl and 245 ml of THF at room temperature. The solution was refluxed for 1 hr and worked up in the conventional manner, giving 17.4 g of basic oil. Dilution with Et_2O precipitated 7.4 g of crystalline solid, mp 112–114°. Processing the mother liquors gave 7.9 g of slightly impure product, mp 97–98°. The first crop was converted to salt **36**.

Compound 37 was prepared from *cis*-methyl (±)-1-methyl-4-phenyl-3-piperidinecarboxylate[3] in the manner of the proceeding experiment but using 47.4 g (0.203 mol) of the ester and 205 ml (0.62 mol) of 3 *M* CH_3MgCl. The crystalline product (54 g) was recrystallized (Et_2O) to give 44.1 g of prisms, mp 110–113°. This base (12 g) gave 9.9 g of once recrystallized salt **37**.

Dehydration of Alcohol 36. A solution of 7.9 g (0.034 mol) of *trans*-carbinol **36** in 50 ml of HOAc was treated with 8 ml of concentrated H_2SO_4 with stirring in 5 min. The solution was heated on the steam bath for 4 hr, cooled, diluted with 40 g of ice, and made basic with 35% aqueous NaOH. Extraction with Et_2O gave 6.2 g of basic oil which was chromatographed on 22 preparative silica plates (20 × 40 cm) using Et_2O–*i*-$PrNH_2$ (97:3) for development. The less polar of the two principal bands furnished 3.5 g of oily 3-isopropylidene-1-methyl-4-phenylpiperidine: nmr ($CDCl_3$) δ 1.73 and 1.85 [2 s, 6, $(CH_3)_2C=$], 2.14 (s, 3, NCH_3), and 7.0–7.65 ppm (m, 5, arom). Its 1,5-naphthalenedisulfonate salt is **38**.

The more polar of the two plate bands furnished 2.2 g of oily *trans*-1-methyl-3-(1-methylvinyl)-4-phenylpiperidine: nmr ($CDCl_3$) δ 1.53 (s, 3, $CH_3C=$), 2.32 (s, 3, NCH_3), 4.64 (s, 2, $CH_2=$), and 7.0–7.5 ppm (m, 5, arom). The HCl salt is **39**.

When the heating period for the dehydration was reduced to 15 min, the more polar product **39** was essentially the only material formed (tlc and nmr).

Dehydration of Alcohol 37. A solution of 12.1 g (0.052 mol) of the *cis*-carbinol **37** in 75 ml of HOAc was treated with 12 ml of concentrated H_2SO_4 in the manner described immediately above but with a heating period of 3 hr. Work-up gave 9.3 g of basic oil which was chromatographed on preparative silica plates. The less polar band gave **38** (24%); the more polar band gave **39** (37%).

When the heating period was reduced to 5 min, the less polar product **38** was essentially the only material formed (tlc and nmr).

Cyclization of Cis Alcohol 37. A mixture of 7.2 g (0.031 mol) of alcohol **37** and 150 ml of PPA was heated at 145–155° for 18 hr. The usual work-up gave an oily base which showed largely a single spot by silica tlc (3:97 *i*-$PrNH_2$–Et_2O). Its HCl salt was triturated with CH_3CN to give 1.37 g of crude **34**. Recrystallization gave the pure salt of Table III.

The filtrate from separation of **34** was concentrated to a residue which was triturated with acetone. Washing the resulting powder with 1:1 acetone–ether gave 2.6 g of crude **35**. This salt was converted to the free base which was chromatographed on eight 20 × 40 cm preparative silica plates. This purified base then furnished the pure salt **35** of Table III.

Cyclization of Olefin 39. A mixture of 5.4 g (0.022 mol) of the trans olefin **39** and 150 ml of PPA was heated at 150–160° for 17 hr and worked up in the usual manner. The basic product afforded 5.6 g of slightly sticky HCl salt. Two recrystallizations from CH_3CN with charcoal treatment gave 4.15 g (77%) of **34**, mp 318–319° dec, identical in crystal form, nmr, ir, and R_f with the product **34** from cyclization of alcohol **37**.

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