Synthesis of *exo*-3-Phenylbicyclo[3.2.1]oct-3-en-2-amine and Related Compounds as Potential Analgesics

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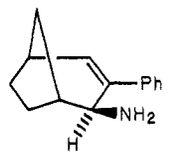
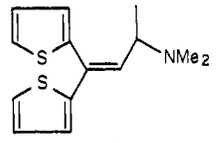
Several analogues (21 and 29–50) of *exo*-3-phenylbicyclo[3.2.1]oct-3-en-2-amine (1) were prepared, a compound that had been found to have marked antinociceptive activity in the inflamed-paw pressure test in rats. Two synthetically versatile methods leading to these compounds are described. In this series, antinociceptive activity increases with increasing size of the amine substituent, reaching an optimum with N(Me)Et (32), but this is always associated with central nervous system (CNS) stimulant activity. The antinociceptive activity of these compounds is most likely due to an action that is similar to that of amphetamine rather than to an interaction with an opiate receptor. The endo diastereoisomer 22 and the benzo analogue 11 were both devoid of antinociceptive and CNS stimulant activity.

In the course of a general screening program, the allylamine 1 was found to be about twice as potent as codeine



1



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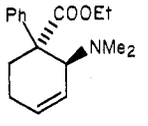


3

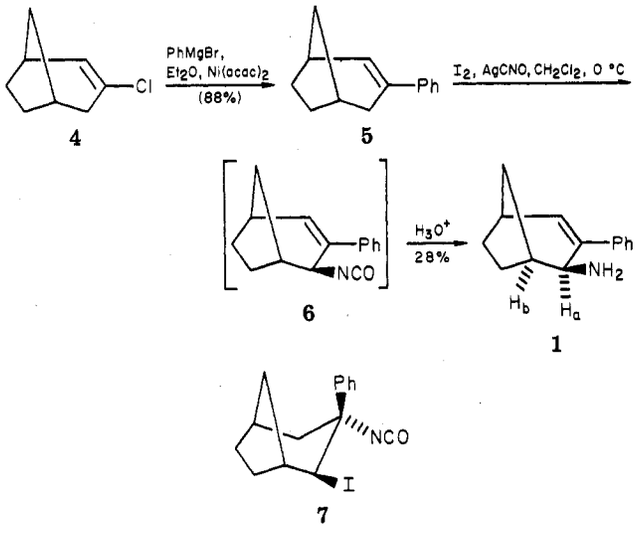
as an antinociceptive agent in the inflamed-paw pressure test in rats. Although other allylamines are known to have analgesic activity, e.g., dimethylthiambutene (2)[1] and Tilidine (3),[2] to our knowledge 1 is the first example of an analgesic containing the 2-arylallylamine moiety. This paper describes the syntheses and pharmacological activities of 1 and some of its analogues.

Chemistry. In an attempt to form the iodo isocyanate 7 from the olefin 5 by reaction with a mixture of iodine and silver cyanate,[3] we obtained the crude allyl isocyanate 6, which was hydrolyzed with aqueous acid to give the *exo*-allylamine 1 (Scheme I). The exo configuration follows from its ^{1}H NMR spectrum, since the coupling constant J_{H_a,H_b} is 3.0 Hz.[4] The olefin 5[5] was prepared by an improved procedure that involved the coupling of the vinyl chloride 4[5a] and phenylmagnesium bromide in the presence of a nickel catalyst.[6]

At the time that this work was being carried out, Stoll et al.[7] reported a similar reaction with the benzo analogue 8 (Scheme II). They suggested that the iodo isocyanate 9 is formed and undergoes loss of HI during transformation to the amine 11 via the carbamate 10. No spectral data were given for 9. In our hands, 8 reacted with iodine and silver cyanate under identical conditions to give the allyl isocyanate 12. It is possible that 9 is formed initially but that this spontaneously eliminated HI to give 12. However, a more likely explanation to account for the formation of 6 and 12 is that an allyl iodide is formed in situ which undergoes syn-SN_2' displacement by NCO^- (Scheme III). We are currently investigating this and other possible mechanisms to account for the formation of 6 and 12 and other products.[8]

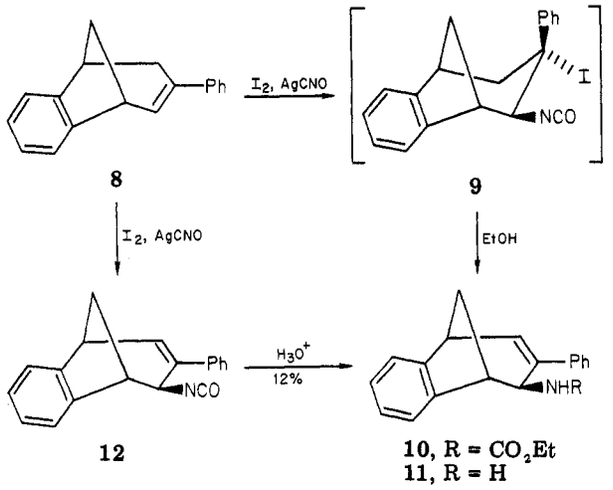
Three general methods were used to prepare analogues of 1. The halides 13 and 14 reacted with amines to give the allylamines 15 (Table I), which were coupled with aryl Grignard reagents in the presence of nickel acetylacetonate to give the arylallylamines 16 (Scheme IV) (method A) (Table II). The *exo*-allylamines 15 are probably formed by a syn-SN_2' displacement, as has been reported for related systems.[9] The coupling reactions were slower than

Scheme I



4 5 6 1 7

Scheme II



8 9 12 10, R = CO_2Et 11, R = H

with the simple halide 4, probably due to complexation of the nickel by the basic nitrogen. Although both 13 and

† Chemistry Department.
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(1) D. W. Adamson and A. F. Green, *Nature (London)*, 165, 122 (1950).
(2) G. Satzinger, *Justus Liebigs Ann. Chem.*, 728, 64 (1969); *ibid.*, 758, 43 (1972).
(3) A. Hassner and C. H. Heathcock, *Org. Synth.*, 51, 112 (1971).
(4) It has been shown that the coupling constant of the allylic proton in exo-substituted bicyclo[3.2.1]octenes is 2–4 Hz, whereas in the corresponding endo compounds the coupling constant is 5–7 Hz: C. W. Jefford, B. Waegell, and K. Ramey, *J. Am. Chem. Soc.*, 87, 2191 (1965); C. W. Jefford, S. Mahayan, J. Waslyn, and B. Waegell, *ibid.*, 87, 2183 (1965).

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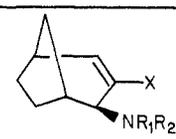
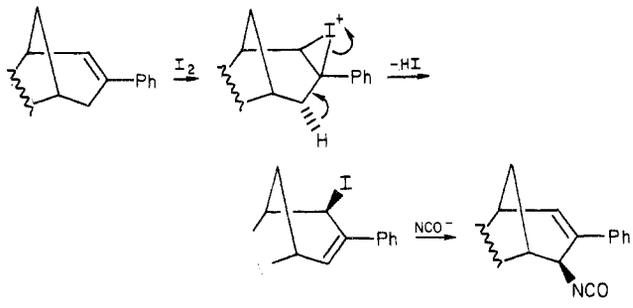
Table I. Physical Properties of *exo*-3-Halobicyclo[3.2.1]oct-3-en-2-amines (15)



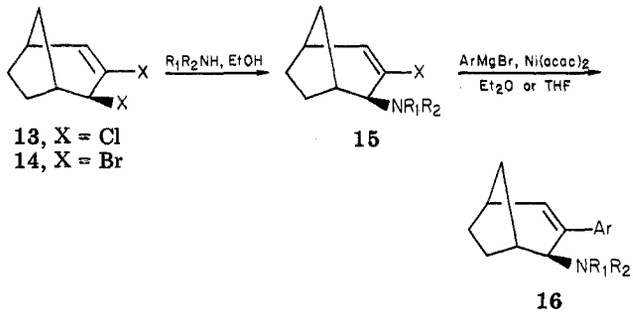
no.	R_1	R_2	X	yield,[a] %	mp[b] or bp, °C (mmHg)	formula	anal.[c]
23	CH_3	CH_3	Br	40[d]	184–186	$C_{10}H_{16}BrN \cdot HCl$	C, H, N
24	H	CH_2CH_3	Br	70[d]	173–174	$C_{10}H_{16}BrN \cdot HCl$	C, H, N, Cl
25	CH_2CH_3	CH_2CH_3	Cl	66	100 (0.01)	$C_{12}H_{20}ClN$	C, H, N, Cl
26	H	c-PrMe[e]	Cl	67	130 (0.1)	$C_{12}H_{18}ClN$	C, H, N
27	H	$CH_2CH(CH_2)_2CH_2$ (O bridge)	Br	71	213–215.5	$C_{13}H_{20}BrNO \cdot HCl$	C, H, N, Cl
28	H	CH_2CH_2Ph	Cl	61	205–206	$C_{16}H_{20}ClN \cdot HCl$	C, H, N, Cl

[a] Yields are of analytically pure material; no attempts were made to optimize yield. [b] Melting points are of hydrochloride salts crystallized from EtOAc–MeOH. [c] Analyses shown are correct to ±0.4%, unless otherwise stated. [d] Prepared in an autoclave. [e] Cyclopropylmethyl.

Scheme III



Scheme IV. Method A

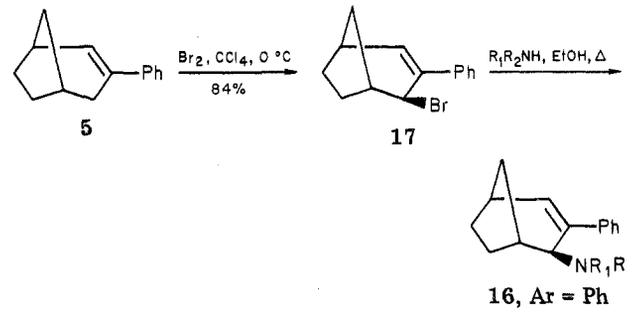


13, X = Cl
14, X = Br

15

16

Scheme V. Method B

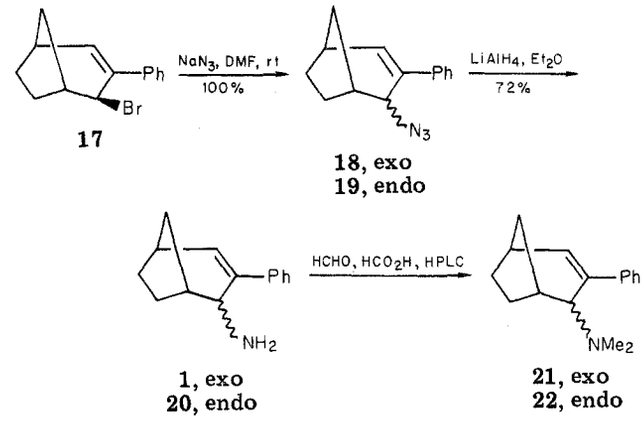


5

17

16, Ar = Ph

Scheme VI



17

18, exo
19, endo

1, exo
20, endo

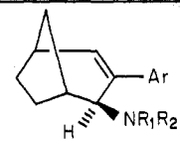
21, exo
22, endo

14 were used to prepare **15**, we found the use of **13** to be more convenient, since this can be prepared in larger quantities more easily than **14**. We found that the best method for preparing the dihalide **13** was that using dichlorocarbene generated from $CHCl_3$ and aqueous NaOH in the presence of benzyltriethylammonium chloride as a phase-transfer catalyst.[10] Other methods for the generation of dichlorocarbene (e.g., $CHCl_3$ and KO-*t*-Bu[11,12] or Cl_3CO_2Et and NaOMe[13]) gave only low yields of **13** and were inconvenient to carry out on a large scale. Addition of dibromocarbene, generated from $CHBr_3$ and KO-*t*-Bu[14] or by phase-transfer catalysis,[10] to norbornene gave only low yields of the dibromide **14**.

Some allylamines **16**, where Ar = Ph, were prepared by reaction of **17** with amines (Scheme V) (method B). We found that **17** was more conveniently prepared by reaction of **5** with bromine in CCl_4 at 0 °C than by the literature method.[5b] Although both methods A and B were used to prepare **16** (Ar = Ph), we found the latter to be more convenient, since the intermediate **17** could be converted in one step into a variety of target compounds in reasonable yield.

(5) Originally prepared in 20% yield from the vinyl chloride (4): (a) C. W. Jefford, J. Gunsher, D. T. Hill, P. Brun, J. Le Gras, and B. Waegell, *Org. Synth.*, **51**, 60 (1971); (b) C. W. Jefford and E. Huang Yen, *Tetrahedron*, **23**, 4549 (1967).
(6) R. J. P. Corriu and J. P. Masse, *J. Chem. Soc., Chem. Commun.*, 144 (1972).
(7) A. P. Stoll, H. Loosli, P. Niklaus, and T. Zardin-Tartaglia, *Helv. Chim. Acta*, **61**, 648 (1978).
(8) A. R. Harris, K. Mills, M. Martin-Smith, P. Murray-Rust, and J. Murray-Rust, *Can. J. Chem.*, **58**, 1847 (1980).
(9) N. Ikota and B. Ganem, *J. Am. Chem. Soc.*, **100**, 351 (1978).
(10) W. Kraus, G. Klein, H. Sadlo, and W. Rothenwohrer, *Synthesis*, 485 (1972).
(11) R. C. De Selms and C. M. Combs, *J. Org. Chem.*, **28**, 2206 (1963).
(12) E. Bergman, *J. Org. Chem.*, **28**, 2210 (1963).
(13) C. W. Jefford, J. Gunsher, D. T. Hill, P. Brun, J. Le Gras, and B. Waegall, *Org. Synth.*, **51**, 60 (1971).
(14) W. R. Moore, W. R. Moser, and J. E. Laprade, *J. Org. Chem.*, **28**, 2200 (1963); C. W. Jefford, *Proc. Chem. Soc.*, 64 (1963).

Table II. Physical Properties of *exo*-3-Arylbicyclo[3.2.1]oct-3-en-2-amines (16)



no.	R_1	R_2	Ar	method	yield,[a] %	mp or bp,[b] °C (mmHg)	refractive index (temp, °C)	formula	anal.
1	H	H	Ph	*d*		249-251[e]		$C_{14}H_{17}N\cdot HCl$	C, H, N, Cl
29	H	CH_3	Ph	*f*		253-254[e]		$C_{15}H_{19}N\cdot HCl$	C, H, N, Cl
21	CH_3	CH_3	Ph	A	65	115-117[e]		$C_{16}H_{21}N\cdot HCl$	C, H, N, Cl
30	CH_3	CH_3	3-CH_3OPh	A	38	170 (0.1)		$C_{17}H_{23}NO$	C, H, N
31	H	CH_2CH_3	Ph	A	41	135 (0.04)	1.5618 (22)	$C_{16}H_{21}N$	C, N; H[h]
32	CH_3	CH_2CH_3	Ph	C	71	130 (0.1)	1.5596 (20)	$C_{17}H_{23}N$	C, H, N
33	CH_3	CH_2CH_3	3-CH_3OPh	A	14	140 (0.01)	1.5583 (22)	$C_{18}H_{25}NO$	C, H, N
34	CH_3	CH_2CH_3	3-HOPh	*i*	30	200 (0.01)	*j*	$C_{17}H_{23}NO$	H, N; C[k]
35	H	$CH_2CH_2CH_3$	Ph	B	51	130 (0.01)	1.5550 (23)	$C_{17}H_{23}N$	C, H, N
36	H	$CH(CH_3)_2$	Ph	B	37	120 (0.02)	1.5520 (22)	$C_{17}H_{23}N$	C, H, N
37	CH_3	$CH_2CH_2CH_3$	Ph	C	76	150 (0.1)	1.5518 (25)	$C_{18}H_{25}N$	C, H, N
38	CH_3	$CH(CH_3)_2$	Ph	C	68	120 (0.04)	1.5527 (24)	$C_{18}H_{25}N$	C, H, N
39	CH_2CH_3	CH_2CH_3	Ph	A	21	120 (0.04)	1.5482 (23)	$C_{18}H_{25}N$	C, H, N
40	H	$CH_2CH{=}CH_2$	Ph	B	56	162.5-164.5[l]		$C_{17}H_{21}N\cdot C_4H_4O_4$	C, H, N
41	CH_3	$CH_2CH{=}CH_2$	Ph	C	93	130 (0.01)	1.5623 (23)	$C_{18}H_{23}N$	C, H, N
42	H	c-PrMe[m]	Ph	A	22	163-165[l]		$C_{18}H_{23}N\cdot C_4H_4O_4$	C, H, N
43	CH_3	c-PrMe[m]	Ph	C	49	135 (0.04)	1.5604 (23)	$C_{19}H_{25}N$	C, H, N
44	H	$CH_2CH_2OCH_3$	Ph	B	41	155 (0.2)	1.5555 (23)	$C_{17}H_{23}NO$	C, H, N
45	CH_3	$CH_2CH_2OCH_3$	Ph	C	32	120 (0.01)	1.5500 (25)	$C_{18}H_{25}NO$	C, H, N
46	H	$CH_2CH_2N(CH_3)_2$	Ph	B	47	150 (0.01)	1.5513 (23)	$C_{18}H_{26}N_2$	C, H, N
47	CH_3	$CH_2CH_2N(CH_3)_2$	Ph	B	41	180 (0.4)	1.5503 (22)	$C_{19}H_{28}N_2$	C, H, N
48		$-(CH_2)_4-$	Ph	B	38	150 (0.1)	1.5742 (25)	$C_{18}H_{23}N$	C, H, N
49	H	$CH_2\overset{\displaystyle O}{\overset{\frown}{C}}H(CH_2)_2CH_2$	Ph	A	12	118-119[l]		$C_{19}H_{25}NO\cdot C_4H_4O_4$	C, H, N
50	H	CH_2CH_2Ph	Ph	A	12	220.5-222.5[e]		$C_{22}H_{25}N\cdot HCl$	C, H, N

[a] Yields are of analytically pure material: no attempt was made to optimize yields. [b] In cases when bulb to bulb distillation was used to afford purification, the refractive index is given as an additional physical constant. [c] Analyses shown are correct to ±0.4%, unless otherwise noted. [d] See text. [e] Hydrochloride salt crystallized from EtOAc–MeOH. [f] Prepared by the reduction of the formamide of 1. [g] C: calcd, 72.84; found, 72.37. [h] H: calcd, 9.31; found, 9.80. [i] Prepared by demethylation of 33 with aqueous HBr. [j] Glassy solid, mp 60-70 °C. [k] C: calcd, 79.33; found, 78.19. MS calcd for $C_{17}H_{23}NO$, 257.1780 (M^+); found, 257.1773. [l] Maleate salt crystallized from EtOAc–MeOH. [m] Cyclopropylmethyl.

A number of tertiary allylamines **16** (R_1 = Me) were prepared by Eschweiler–Clarke methylation of **16** (R_1 = H) (method C).

We considered it important to prepare an example of an *endo*-allylamine, since it is well documented that small changes in stereochemistry can lead to radical changes in biological activity.[15] To this end, we investigated the reaction of **17** with less bulky nucleophiles to try to effect displacement of the halogen by attack from the more hindered endo face. Thus, **17** reacted with sodium azide in DMF to give a mixture of the epimeric azides **18** and **19** (exo/endo ratio 4:1 by ^1H NMR spectroscopy) (cf. ref 16), which was reduced without purification to give the epimeric allylamines **1** and **20** (Scheme VI). We were unable to separate these epimers,[17] so the mixture was therefore converted into the tertiary amines **21** and **22**, from which **22** was separated by HPLC.

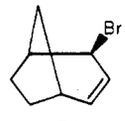
Results and Discussion

The compounds described in this paper were tested for antinociceptive activity in the inflamed-paw pressure test in the rat (Table III). Those compounds having an ED_{50} of less than 30 mg/kg po and compounds **36**, **39**, **42**, **44**, and **49** were further tested in the acetylcholine-induced writhing test in the mouse. Full details of these methods have been described previously.[18] In this series in the rat, activity increases with increasing size of the amine function, reaching an optimum with N(Me)Et (**32**). Larger substituents result in reduced activity. Compounds with substituents in the aromatic ring were less active than their unsubstituted counterparts. The benzo analogue **11** and the *endo*-amine **22** were both inactive.

The results obtained (Table III) show that the compounds that possess antinociceptive activity in the rat and mouse also possess observable behavioral stimulation. There was a good correlation between activity in the inflamed-paw pressure test and the intensity of CNS stim-

(15) R. E. Lister, *J. Pharm. Pharmacol.*, **16**, 364 (1964); R. L. Clarke, A. J. Gambino, and S. J. Daum, *J. Med. Chem.*, **17**, 1040 (1974).

(16) This is in contrast to the related allyl bromide (**51**), which reacts with NaN_3 in aqueous CCl_4 to give the *exo*-azide only: L. A. Spurlock and R. J. Schultz, *J. Am. Chem. Soc.*, **92**, 6302 (1970).



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(17) It was not possible to separate **1** and **20** either by HPLC, column chromatography, or fractional crystallization of their hydrochloride salts.

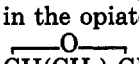
(18) M. B. Tyers, *Br. J. Pharmacol.*, **69**, 503 (1980).

Table III. Antinociceptive and Behavioral Stimulant Effects of *exo*-3-Arylbicyclo[3.2.1]oct-3-en-2-amines

	antinociceptive act.: ED_{50} (95% CL), mg/kg po		
	inhibn of acetylcholine writhing (mouse)	inflamed paw pressure threshold (rat)	behavioral stimulant act. (rat),[a] mg/kg po
1	8.3 (0.5-23.6)	⩾10.0 [NB 3.2 (1.4-6.8) sc]	25 (0) [25 sc (++)]
29	4.0 (1.7-8.3)	13.4 (3.9-41.0)	25 (+ → ++)
21	3.9 (0.03-16.3)	2.9 (0.4-9.4)	25 (±) 50 (++)
30	34.4 (24.5-50.2)	7.8 (3.1-18.1)	25 (±) 50 (++)
31	15.6 (7.6-34.8)	3.1 (1.5-5.5)	25 (± → +) 50 (++)
32	11.8 (6.0-23.9)	1.4 (0.2-4.8)	25 (++)
33	30.6 (17.1-55.2)	10.4 (2.0-56.3)	25 (±) 50 (+ → ++)
34	NT	>30	25 (0)
35	NT	>30	25 (± → +)
36	15.4 (5.9-36.7)	>30	25 (±) 50 (±)
37	NT	⩾30	25 (0)
38	NT	>30	25 (0)
39	2.4 (0.9-5.3)	>30	25 (± → +)
40	13.7 (7.7-23.7)	11.0 (2.8-63.8)	25 (±) 50 (+)
41	NT	⩾30	25 (0)
42	4.1 (1.1-13.7)	>30	25 (0)
43	NT	>30	25 (±) 50 (± → +)
44	27.7 (11.7-72.4)	>30	50 (±)
45	NT	>30	25 (0)
46	31.0 (17.3-55.9)	18.1 (4.3-125)	50 (0)
47	NT	>30	25 (0)
48	19.0 (10.4-33.8)	15.7 (3.7-102)	25 (+) 50 (++)
49	>30	⩾30	50 (0)
50	NT	>30	50 (0)
amphetamine	1.6 (0.9-2.7)	2.1 (0.4-9.2)	6.25 (± → +) 12.5 (++)
codeine	10.3 (4.2-15.7)	5.7 (1.8-18.3)	50 (0)

[a] 0 = inactive; ±/+/++ = slight/moderate/marked CNS stimulation. NT = not tested.

ulation in the rat. The antinociceptive activities in the mouse and rat were generally in good agreement. Exceptions to this were compounds **1**, **29**, **39**, and **42**, which were much less active orally in the rat than in the mouse. These latter findings are probably a result of poor oral absorption. For example, following subcutaneous dosing, the amine **1** produced a potent antinociceptive effect and marked CNS stimulation.

It seems unlikely that the present compounds produce analgesia via interaction with an opiate receptor. In the inflamed-paw pressure test, pretreatment with naloxone, 2 mg/kg sc, had no effect on the antinociceptive activity of compounds **32**, **21**, **31**, and amphetamine in the rat. In addition, none of the compounds up to a concentration of 1×10^{-4}M inhibited contractions of the longitudinal muscle of the guinea pig ileum or the mouse vas deferens preparations induced by electrical field stimulation. Substitution on nitrogen with groups that lead to increased potency in the opiate analgesics, e.g., CH_2CH_2Ph (**49**) and CH_2- 
$CH(CH_2)_2CH_2$ (**50**), resulted in a loss of activity, as did the introduction of a phenolic *m*-OH group (**34**). Furthermore, there was no indication of opiate receptor antagonist activity in compounds with cyclopropylmethyl (**42** and **43**) or allyl (**40** and **41**) substituents on nitrogen.[19]

The mechanism of action of these compounds was further studied in rats in which the nigrostriatal dopaminergic pathway has been lesioned unilaterally with a discrete injection of 6-hydroxydopamine according to methods described by Ungerstedt.[20] In these rats, amphetamine injected intraperitoneally caused the rats to rotate toward the lesioned side, which is consistent with its known action on dopamine release. Similarly, the most potent antinociceptive agent in the series presented here, **32**, at a dose of 5 mg/kg, ip, also caused the rats to rotate toward the lesioned side.

Conclusion

The antinociceptive and behavioral stimulant activities of the *exo*-3-phenylbicyclo[3.2.1]oct-3-en-2-amines reported are most likely due to an action that is similar to that of amphetamine. The analgesic and stimulant properties of amphetamine and related compounds are well known,[21] although their mechanism of action remains obscure. Unfortunately, none of the compounds tested possessed antinociceptive activity without accompanying CNS stimulant activity.

Experimental Section

Pharmacology. Groups of six animals per dose of compound were tested on two or three separate occasions for each ED_{50} determination. The data obtained were accumulated for regression analysis and ED_{50} calculations giving total dose groups of 12 or 18 animals. All testing was carried out blind. Further tests were carried out in groups of three rats to determine the effects of these compounds on normal behavior. Only the more prominent

(19) P. Portoghese, *J. Med. Chem.*, 8, 609 (1965).

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changes in behavior were noted; these were locomotor activity, touch response and stereotypy manifested by repetitive head and limb movements, sniffing, licking, and gnawing. Effects on opiate receptors in vitro were determined in the isolated guinea pig ileum and mouse vas deferens preparations according to methods described by Gyang and Kosterlktz[22] and Hughes, Kosterlitz, and Leslie.[23]

Chemistry. Melting points were determined on a Townson and Mercer apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian Associates EM 390 spectrometer. IR spectra were recorded on a Perkin–Elmer 357 grating spectrophotometer, UV spectra on a Perkin-Elmer 402 spectrophotometer, and mass spectra on a Kratos-AE1 MS30 spectrophotometer.

3-Phenylbicyclo[3.2.1]oct-2-ene (5). A solution of PhMgBr [prepared from Mg (9.6 g, 0.4 mol) and PhBr (62 g, 0.4 mol)] in Et_2O (150 mL) was added dropwise with cooling (0 °C) under N_2 to a stirred mixture of nickel(II) acetylacetonate (0.3 g) and 4[5a] (37.5 g, 0.267 mol). The mixture was stirred at room temperature for 20 h and then 2 M HCl (200 mL) was added dropwise at 0 °C. The organic phase was separated, and the aqueous phase was extracted with Et_2O (2 × 200 mL). The extracts were combined, dried ($MgSO_4$), and evaporated. The residue was distilled to give 5: yield 43.2 g (88%); bp 109–113 °C (1.5 mmHg) [lit.[5b] bp 80 °C (0.5 mmHg)].

***exo*-3-Phenylbicyclo[3.2.1]oct-3-en-2-amine (1).** I_2 (57 g, 0.22 mol) was added in portions (~5 g) over 1 h to a stirred solution of 5 (43 g, 0.23 mol) and AgNCO (43 g, 0.22 mol) in CH_2Cl_2 (400 mL) at 0 °C under N_2. The mixture was stirred at 0 °C for 4 h and kept at 0–5 °C overnight. The solid was filtered off, and the filtrate was washed with 8% $Na_2S_2O_3$ (250 mL), dried ($MgSO_4$), and evaporated to give a pale yellow oil (45 g). This crude oil contains approximately 50% 6: ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H, aromatic), 6.31 (d, J = 7 Hz, 1 H, C=CH), 4.12 (d, J = 2.5 Hz, 1 H, CHNCO), 2.60–1.00 (m, 8 H, aliphatic); IR (liquid film) ν_{max} 2260 (NCO) cm^{-1}. The oil was dissolved in acetone (400 mL) and treated with concentrated HCl (100 mL) at 0 °C. The solution was kept at room temperature overnight and then evaporated in vacuo. The residue was partitioned between H_2O (300 mL) and EtOAc (400 mL), and some insoluble material was filtered off. The aqueous layer was separated, washed with EtOAc (300 mL), and then basified with 2 M NaOH and extracted with EtOAc (3 × 200 mL). The extracts were combined, dried ($MgSO_4$), and evaporated to ca. 200 mL in vacuo. The solution was treated with 8% ethereal HCl until no more precipitate formed, and the salt was filtered off and crystallized from a mixture of MeOH and EtOAc to give 1·HCl as a white powder: yield 14.4 g (28%); mp 249–251 °C dec; ^1H NMR (D_2O) δ 7.55 (br s, 5 H, aromatic), 6.60 (d, J = 7 Hz, 1 H, C*H*=CPh), 4.32 (d, J = 3.5 Hz, 1 H, C*H*NH_2), 2.90–1.40 (m, 8 H, remaining aliphatic); UV λ_{max} (EtOH) 244 nm (ε 11 100). Anal. ($C_{14}H_{17}N$·HCl) C, H, N, Cl.

***exo*-5,6-Dihydro-7-phenyl-5,9-methano-9*H*-benzocyclohepten-6-amine Hydrochloride (11).** A procedure identical with that for making 1 was used for converting 5 g of 8 into 11·HCl: yield 0.7 g (12%); mp 310–313 °C (lit.[7] mp 307–320 °C); via crude 12 (5 g): IR ν_{max} 2250 (NCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.48 (d, J = 7 Hz, 1 H, C*H*=CPh), 4.41 (d, J = 3 Hz, 1 H, CHNCO).

General Procedures for the Preparation of *exo*-3-Arylbicyclo[3.2.1]oct-3-en-2-amines (16; Table II). Method A (Scheme IV). Preparation of *exo*-3-Halobicyclo[3.2.1]oct-3-en-2-amines (15). A solution of 13 or 14 (0.085 mol) and the appropriate amine (0.18 mol) in EtOH (50 mL) was heated for 48 h under reflux. The solution was evaporated to dryness, and the residue was dissolved in 1 M HCl (100 mL) and washed with Et_2O (3 × 100 mL). The aqueous solution was basified with 2 M NaOH and extracted with Et_2O (3 × 100 mL). The extracts were combined, dried (Na_2SO_4), and evaporated, and the residue was distilled to give the allylamines 15 as colorless oils (Table I). Reactions with Me_2NH and $EtNH_2$ were carried out in an autoclave.

Conversion of 15 into *exo*-3-Arylbicyclo[3.2.1]oct-3-en-2-amines (16). A solution of the appropriate arylmagnesium bromide (0.094 mol) in dry THF (50 mL) was added dropwise to a mixture of 15 (0.017 mol) and nickel(II) acetylacetonate (100 mg) in dry THF (15 mL) at 0 °C under N_2. The mixture was heated under reflux for 24 h and then cooled. Saturated NH_4Cl (200 mL) was added with cooling until all the precipitated solid had dissolved. The solution was extracted with ether (3 × 200 mL), and the extracts were combined and extracted with 2 M HCl (3 × 75 mL). The aqueous solution was washed with ether (200 mL), basified with 2 M NaOH, and extracted with ether (3 × 100 mL). The extracts were combined, dried (Na_2SO_4), and evaporated, and the residue was distilled in vacuo to give the allylamines 16.

Method B (Scheme V). *exo*-4-Bromo-3-phenylbicyclo[3.2.1]oct-2-ene (17). Br_2 (11.8 g, 0.067 mol) was added dropwise to a solution of 5 (12.5 g, 0.067 mol) in CCl_4 (100 mL) at 0 °C under N_2. The solution was stirred at 0 °C for 1 h and then evaporated, and the residue was distilled in vacuo to give 17 as a pale orange oil: yield 15.1 g (84%); bp 120 °C (0.5 mmHg) [lit.[5b] bp 125 °C (1 mmHg)].

Reaction of 17 with Amines. A solution of 17 (0.005 mol) and the appropriate amine (0.02 mol) in EtOH (10 mL) was heated under reflux for 24 h. The solution was evaporated to dryness, and the residue was dissolved in 2 M HCl (30 mL). The solution was washed with Et_2O (3 × 50 mL), basified with 2 M NaOH, and extracted with Et_2O (3 × 50 mL). The extracts were combined, dried ($MgSO_4$), and evaporated, and the residue was distiled in vacuo to give the allylamines 16.

Method C. Methylation of Allylamines 16 (R_1 = H). A solution of 16 (R_1 = H) (0.003 mol) in 40% aqueous HCHO (3 mL) and 98% HCO_2H (3 mL) was heated at 100 °C for 4 h. The solution was cooled, poured into 2 M NaOH (30 mL), and extracted with Et_2O (3 × 50 mL). The extracts were combined, dried (Na_2SO_4), and evaporated, and the residue was distilled in vacuo to give the allylamines 16 (R_1 = Me).

***endo*-3-Phenylbicyclo[3.2.1]oct-3-en-2-amine (22) (Scheme VI). *exo*- and *endo*-4-Azido-3-phenylbicyclo[3.2.1]oct-2-ene (18 and 19).** A mixture of 17 (3 g, 0.013 mol) and NaN_3 (0.75 g, 0.015 mol) in dry DMF (20 mL) was stirred at room temperature for 1.5 h and then poured into H_2O (300 mL). The solution was extracted with Et_2O (3 × 150 mL), and the extracts were combined, washed with H_2O (5 × 100 mL), dried ($MgSO_4$), and evaporated to give a mixture of 18 and 19 in the ratio 4:1 as a pale brown oil: yield 2.5 g (100%); ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H, aromatic), 6.48 (d, J = 6 Hz, C*H*=CPh, exo isomer), 6.28 (d, J = 6 Hz, C*H*=CPh, endo isomer), 4.88 (d, J = 5 Hz, CHN_3, endo isomer), 4.00 (d, J = 3, Hz, CHN_3, exo isomer), 2.70 (m, 2 H, 2 CH), 2.20–1.20 (m, 6 H, 3 CH_2); IR (liquid film) ν_{max} 2190 (N_3) cm^{-1}.

***exo*- and *endo*-3-Phenylbicyclo[3.2.1]oct-3-en-2-amine (1 and 20).** A solution of the epimeric mixture 18 and 19 (28 g, 0.125 mol) in dry Et_2O (70 mL) was added dropwise over 1 h to a stirred suspension of $LiAlH_4$ (5.5 g, 0.14 mol) in dry Et_2O (200 mL) at 0 °C under N_2. The mixture was stirred for 3 h at room temperature, and then 2 M NaOH (10 mL) was added dropwise at 0 °C. The solid was filtered off, and the filtrate was dried (Na_2SO_4) and then treated wiith 8% ethereal HCl until no more precipitate formed. The salt was filtered off and dried to give a 4:1 mixture of 1·HCl and 20·HCl as a cream powder: yield 19 g (72%); ^1H NMR of the free base ($CDCl_3$), in addition to the signals for the exo-isomer 1 (see above), the endo-isomer 20 was shown by the signals at δ 6.10 (d, J = 6 Hz, C*H*=CPh) and 4.23 (d, J = 5 Hz, C*H*NH_2).

***N,N*-Dimethyl-3-phenylbicyclo[3.2.1]oct-3-en-2-amine (22).** A solution of the epimeric mixture 1·HCl and 20·HCl (14 g, 0.06 mol) in 98% HCO_2H (40 mL) and 40% aqueous HCHO (40 mL) was heated at 100 °C for 24 h, cooled, and then poured into 2 M NaOH (500 mL). The mixture was extracted with Et_2O (3 × 200 mL), and the extracts were combined, dried (Na_2SO_4), and evaporated. The residual oil (15 g) was dissolved in 2 M HCl (250 mL), and the solution washed with EtOAc (2 × 150 mL) and then basified with solid K_2CO_3. The product was extracted with EtOAc (3 × 150 mL), and the extracts were combined, dried (Na_2SO_4), and evaporated to give a mixture of the exo-isomer 21 and the endo-isomer 22 as a pale yellow oil (9 g). This mixture was separated by HPLC on a Waters Associates Preparative LC system 500 eluting with 1% EtOH in *n*-hexane (100 mL/min)

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on two "Prep Pak" columns to give **22** (0.5 g) as the faster running component. This material was dissolved in EtOAc and treated with a solution of maleic acid (250 mg) in MeOH. The solution was concentrated to give a white precipitate, which was filtered off and crystallized from a mixture of MeOH and EtOAc to give **22** maleate as a white powder: yield 0.25 g (1.2%); mp 151–152 °C; ^{1}H NMR (D_2O) δ 7.40 (m, 5 H, aromatic), 6.46 (d, J = 7 Hz, 1 H, C*H*=CPh), 5.00 (d, J = 4.5 Hz, 1 H, C*H*NMe_2), 6.3 (s, 2 H, maleic acid), 2.97 (br s, 1 H, =CHC*H*<), 2.70 (s, 6 H, NMe_2), 2.68 (br s, 1 H, Me_2NCC*H*<), 2.10–1.70 (m, 6 H, remaining CH_2); UV λ_{max} (EtOH) 236 nm (ε 13 300). Anal. ($C_{16}H_{21}N \cdot C_4H_4O_4$) C, H; N: calcd, 4.1; found, 5.0. MS Calcd for $C_{16}H_{21}N$, 227. 1674 (M^+); found, 227.1677.

Registry No. **1**·HCl, 75590-28-2; **4**, 35242-17-2; **5**, 16917-83-2; **6**, 83435-88-5; **8**, 66720-22-7; **11**·HCl, 66720-27-2; **12**, 83435-89-6; **13**, 2394-47-0; **14**, 2404-39-9; **17**, 16917-84-3; **18**, 83435-90-9; **19**, 83435-91-0; **20**·HCl, 83435-92-1; **21**·HCl, 83435-93-2; **22**·HCl, 83435-96-5; **22** maleate, 83435-95-4; **23**·HCl, 83435-97-6; **24**·HCl, 83435-98-7; **25**, 83435-99-8; **26**, 83436-00-4; **27**·HCl, 83436-01-5; **28**·HCl, 83436-02-6; **29**·HCl, 83436-03-7; **30**, 83436-04-8; **31**, 83436-05-9; **32**, 83436-06-0; **33**, 83436-07-1; **34**, 83436-08-2; **35**, 83436-09-3; **36**, 83447-47-6; **37**, 83436-10-6; **38**, 83436-11-7; **39**, 83436-12-8; **40** maleate, 83436-14-0; **41**, 83436-15-1; **42** maleate, 83436-17-3; **43**, 83436-18-4; **44**, 83436-19-5; **45**, 83436-20-8; **46**, 83436-21-9; **47**, 83436-22-0; **48**, 83436-23-1; **49** maleate, 83436-25-3; **50**·HCl, 83436-26-4.

New Carboxyalkyl Inhibitors of Brain Enkephalinase: Synthesis, Biological Activity, and Analgesic Properties

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New carboxyalkyl compounds derived from Phe-Leu and Phe-Ala were synthesized and checked as inhibitors of "enkephalinase", a metalloendopeptidase cleaving the Gly^3–Phe^4 bond of enkephalins from mouse striatal membranes. Differential recognition of both brain enkephalinase and angiotensin-converting enzyme (ACE) catalytic sites by these carboxylalkyl compounds lead to potent ($K_I \approx 0.5$ μM), competitive and selective inhibitors of the enkephalin-degrading enzyme. The most interesting compound, *N*-[(*RS*)-2-carboxy-3-phenylpropanoyl]-L-leucine (**3**, $K_I = 0.34$ μM), is 10 000 times more potent on enkephalinase than on ACE activities. Intracerebroventricular (icv) injection of **3** in mice leads to a high potentiation of the analgesic effect of the exogenously administered D-Ala^2-Met-enkephalin, evidencing the in vivo inhibition of enkephalinase. Moreover, icv administration of **3** alone induces a dose-dependent analgesia in mice measured on both hot-plate and writhing tests. In the former assay, the ED_{50} was approximately 10 μg per animal, slightly higher than that of thiorphan. All the antinociceptive effects were antagonized by naloxone, demonstrating the involvement of enkephalins in analgesia and their in vivo protection from enkephalinase by **3**. The described compounds can be considered as first examples of a new series of analgesics and potentially psychoactive agents.

A large number of results,[1,2] including the recently reported release of enkephalins following tooth pulp stimulation,[3] evidenced the involvement of the endogenous pentapeptides, Tyr-Gly-Gly-Phe-Met (Met-E) and Tyr-Gly-Gly-Phe-Leu (Leu-E), in the regulation of nociceptive stimuli through a specific interaction with opiate receptors, most probably of μ subtypes.[4] According to their assumed neurotransmitter role, these endogenous peptides seem to be quickly removed from the synaptic cleft through the action of degrading enzymes. Various brain peptidases, including aminopeptidases[5-8] and the two peptidyldipeptide hydrolases, "enkephalinase"[9-13] and angiotensin-converting enzyme (ACE),[14] are able to degradate enkephalins by cleavage of the Gly^3–Phe^4 bond. However, the relevance of enkephalinase in the physiological regulation of enkephalinergic transmission is supported by (1) its regional distribution and subcellular localization, which parallel those of opiate receptors and correlate with enkephalins content;[15] (2) the changes in enzymatic activity following chronic morphine treatment;[9] and (3) the strong analgesic activity of enkephalin analogues protected from degradation by enkephalinase.[16]

Enkephalinase is a Zn metalloenzyme whose specificity is essentially ensured by specific interactions of the released C-terminal dipeptides Phe-Met or Phe-Leu.[17] So, enkephalinase contains an hydrophobic S_1' subsite, specific for aromatic residues, and a lipophilic S_2' subsite without a marked selectivity except its aversion for proline and

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