

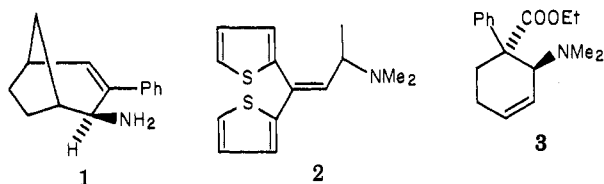
Synthesis of *exo*-3-Phenylbicyclo[3.2.1]oct-3-en-2-amine and Related Compounds as Potential Analgesics

Alan Harris,[†] David Middlemiss,^{*,†} Keith Mills,[†] Alma J. Gower,[‡] and Michael B. Tyers[‡]

Chemistry Department and Pharmacology Department, Glaxo Group Research Ltd., Ware, Hertfordshire, SG12 0DJ, England.
Received March 1, 1982

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



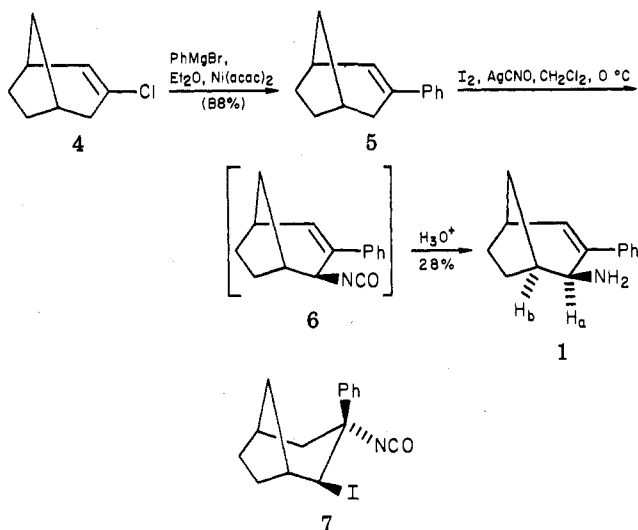
as an antinociceptive agent in the inflamed-paw pressure test in rats. Although other allylamines are known to have analgesic activity, e.g., dimethylthiambutene (2)¹ and Tilidine (3),² to our knowledge 1 is the first example of an analgesic containing the 2-arylallylamine moiety. This paper describes 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 ¹H NMR spectrum, since the coupling constant J_{H_a, H_b} is 3.0 Hz.⁴ The olefin 5⁵ was prepared by an improved procedure that involved the coupling of the vinyl chloride 4^{6a} and phenylmagnesium bromide in the presence of a nickel catalyst.⁶

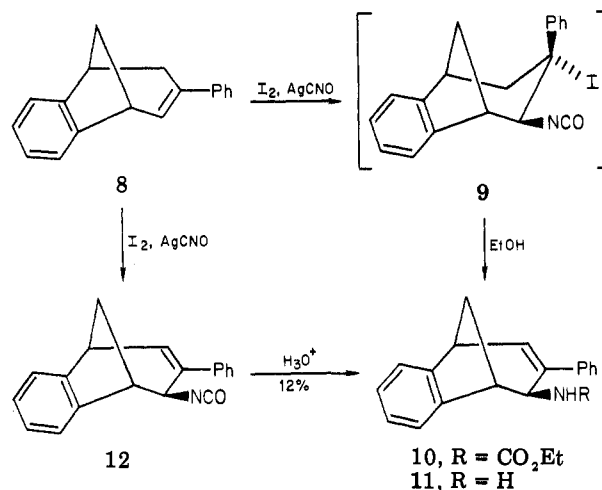
At the time that this work was being carried out, Stoll et al.⁷ reported a similar reaction with the benzo analogue 8 (Scheme II). They suggested that the iodo isocyanate 9 is formed and undergoes loss of HI during transformation to the amine 11 via the carbamate 10. No spectral data were given for 9. 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-SN₂' 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-SN₂' displacement, as has been reported for related systems.⁹ The coupling reactions were slower than

Scheme I



Scheme II



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

- (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).

[†]Chemistry Department.

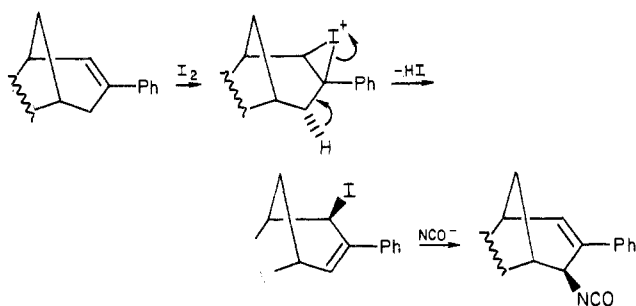
[‡]Pharmacology Department.

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

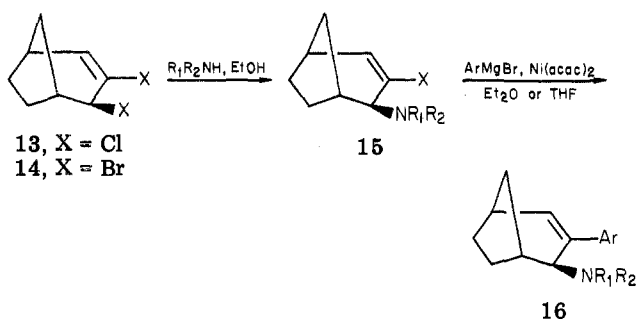
no.	R ₁	R ₂	X	yield, ^a %	mp ^b or bp, ^c (mmHg), °C	formula	anal. ^c
23	CH ₃	CH ₃	Br	40 ^d	184-186	C ₁₀ H ₁₆ BrN·HCl	C, H, N
24	H	CH ₂ CH ₃	Br	70 ^d	173-174	C ₁₀ H ₁₆ BrN·HCl	C, H, N, Cl
25	CH ₂ CH ₃	CH ₂ CH ₃	Cl	66	100 (0.01)	C ₁₂ H ₂₀ ClN	C, H, N, Cl
26	H	c-PrMe ^e	Cl	67	130 (0.1)	C ₁₂ H ₁₈ ClN	C, H, N
27	H		Br	71	213-215.5	C ₁₃ H ₂₀ BrNO·HCl	C, H, N, Cl
28	H	CH ₂ CH ₂ Ph	Cl	61	205-206	C ₁₆ H ₂₀ ClN·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

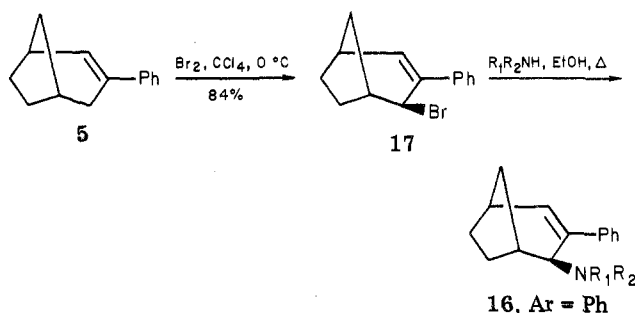


Scheme IV. Method A

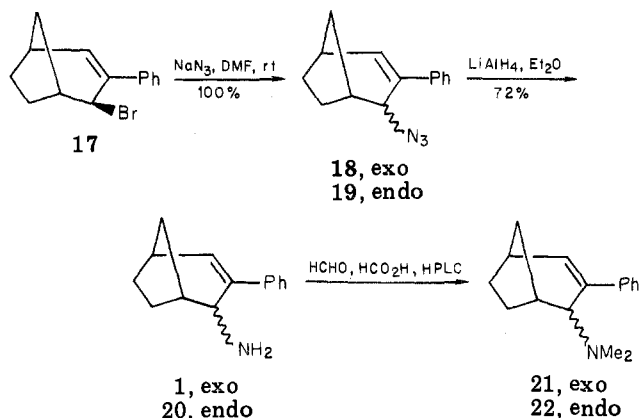


14 were used to prepare 15, we found the use of 13 to be more convenient, since this can be prepared in larger quantities more easily than 14. We found that the best method for preparing the dihalide 13 was that using dichlorocarbene generated from CHCl₃ and aqueous NaOH in the presence of benzyltriethylammonium chloride as a phase-transfer catalyst.¹⁰ Other methods for the generation of dichlorocarbene (e.g., CHCl₃ and KO-*t*-Bu^{11,12} or

Scheme V. Method B



Scheme VI

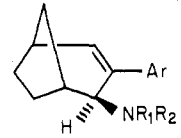


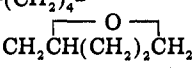
Cl₃CO₂Et and NaOMe¹³) gave only low yields of 13 and were inconvenient to carry out on a large scale. Addition of dibromocarbene, generated from CHBr₃ and KO-*t*-Bu¹⁴ or by phase-transfer catalysis,¹⁰ to norbornene gave only low yields of the dibromide 14.

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 CCl₄ 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. Waegell, *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	<i>d</i>		249–251 ^e		C ₁₄ H ₁₇ N·HCl	C, H, N, Cl
29	H	CH ₃	Ph	<i>f</i>		253–254 ^e		C ₁₅ H ₁₉ N·HCl	C, H, N, Cl
21	CH ₃	CH ₃	Ph	A	65	115–117 ^e		C ₁₆ H ₂₁ N·HCl	C, H, N, Cl
30	CH ₃	CH ₃	3-CH ₃ OPh	A	38	170 (0.1)		C ₁₇ H ₂₃ NO	C, H, N
31	H	CH ₂ CH ₃	Ph	A	41	135 (0.04)	1.5618 (22)	C ₁₆ H ₂₁ N	C, N; H ^h
32	CH ₃	CH ₂ CH ₃	Ph	C	71	130 (0.1)	1.5596 (20)	C ₁₇ H ₂₃ N	C, H, N
33	CH ₃	CH ₂ CH ₃	3-CH ₃ OPh	A	14	140 (0.01)	1.5583 (22)	C ₁₈ H ₂₅ NO	C, H, N
34	CH ₃	CH ₂ CH ₃	3-HOPh	<i>i</i>	30	200 (0.01)	<i>j</i>	C ₁₇ H ₂₃ NO	H, N; C ^k
35	H	CH ₂ CH ₂ CH 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 ₂ CH ₂ CH 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 ₂ CH ₃	CH ₂ CH ₃	Ph	A	21	120 (0.04)	1.5482 (23)	C ₁₈ H ₂₅ N	C, H, N
40	H	CH ₂ CH=CH ₂	Ph	B	56	162.5–164.5 ^l		C ₁₇ H ₂₁ N· C ₄ H ₄ O ₄	C, H, N
41	CH ₃	CH ₂ CH=CH ₂	Ph	C	93	130 (0.01)	1.5623 (23)	C ₁₈ H ₂₃ N	C, H, N
42	H	<i>c</i> -PrMe ^m	Ph	A	22	163–165 ^l		C ₁₈ H ₂₃ N· C ₄ H ₄ O ₄	C, H, N
43	CH ₃	<i>c</i> -PrMe ^m	Ph	C	49	135 (0.04)	1.5604 (23)	C ₁₉ H ₂₅ N	C, H, N
44	H	CH ₂ CH ₂ OCH ₃	Ph	B	41	155 (0.2)	1.5555 (23)	C ₁₇ H ₂₃ NO	C, H, N
45	CH ₃	CH ₂ CH ₂ OCH ₃	Ph	C	32	120 (0.01)	1.5500 (25)	C ₁₈ H ₂₅ NO	C, H, N
46	H	CH ₂ CH ₂ N(CH ₃) ₂	Ph	B	47	150 (0.01)	1.5513 (23)	C ₁₈ H ₂₅ N ₂	C, H, N
47	CH ₃	CH ₂ CH ₂ N(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		Ph	A	12	118–119 ^l		C ₁₉ H ₂₅ NO· C ₄ H ₄ O ₄	C, H, N
50	H	CH ₂ CH ₂ Ph	Ph	A	12	220.5–222.5 ^e		C ₂₂ H ₂₅ N·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 C₁₇H₂₃NO, 257.1780 (M⁺); found, 257.1773. ^l Maleate salt crystallized from EtOAc-MeOH. ^m Cyclopropylmethyl.

A number of tertiary allylamines 16 (R₁ = Me) were prepared by Eschweiler-Clarke methylation of 16 (R₁ = 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.

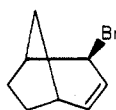
Results and Discussion

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 ED₅₀ 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 NaN₃ in aqueous CCl₄ to give the *exo*-azide only: L. A. Spurlock and R. J. Schultz, *J. Am. Chem. Soc.*, **92**, 6302 (1970).



51

(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 (±)
30	34.4 (24.5-50.2)	7.8 (3.1-18.1)	50 (++)
31	15.6 (7.6-34.8)	3.1 (1.5-5.5)	25 (±)
32	11.8 (6.0-23.9)	1.4 (0.2-4.8)	50 (++)
33	30.6 (17.1-55.2)	10.4 (2.0-56.3)	25 (++)
34	NT	>30	25 (±)
35	NT	>30	50 (+ → ++)
36	15.4 (5.9-36.7)	>30	25 (0)
37	NT	>30	25 (± → +)
38	NT	>30	50 (++)
39	2.4 (0.9-5.3)	>30	25 (±)
40	13.7 (7.7-23.7)	11.0 (2.8-63.8)	25 (± → +)
41	NT	>30	50 (+)
42	4.1 (1.1-13.7)	>30	25 (0)
43	NT	>30	25 (0)
44	27.7 (11.7-72.4)	>30	25 (±)
45	NT	>30	50 (±)
46	31.0 (17.3-55.9)	18.1 (4.3-125)	25 (0)
47	NT	>30	50 (0)
48	19.0 (10.4-33.8)	15.7 (3.7-102)	25 (0)
49	>30	>30	25 (+)
50	NT	>30	50 (++)
amphetamine	1.6 (0.9-2.7)	2.1 (0.4-9.2)	50 (0)
codeine	10.3 (4.2-15.7)	5.7 (1.8-18.3)	6.25 (± → +) 12.5 (++) 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., CH₂CH₂Ph (49) and CH₂-
 $\begin{array}{c} \text{O} \\ \text{---} \\ \text{CH}(\text{CH}_2)_2\text{CH}_2 \end{array}$ (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 ED₅₀ determination. The data obtained were accumulated for regression analysis and ED₅₀ 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

(20) U. Ungerstedt, *Acta Physiol. Scand. Suppl.*, 367 (1971).

(21) E. J. Fellows and G. E. Ulliyot, in "Medicinal Chemistry", Vol. 1, C. M. Suter, Ed., Wiley, New York, 1954.

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

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 Kosterlitz²² 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 Et₂O (150 mL) was added dropwise with cooling (0 °C) under N₂ 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 Et₂O (2 × 200 mL). The extracts were combined, dried (MgSO₄), 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).** I₂ (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 CH₂Cl₂ (400 mL) at 0 °C under N₂. 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% Na₂S₂O₃ (250 mL), dried (MgSO₄), and evaporated to give a pale yellow oil (45 g). This crude oil contains approximately 50% 6: ¹H NMR (CDCl₃) 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 H₂O (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 (MgSO₄), 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 (D₂O) δ 7.55 (br s, 5 H, aromatic), 6.60 (d, *J* = 7 Hz, 1 H, CH=CPh), 4.32 (d, *J* = 3.5 Hz, 1 H, CHNH₂), 2.90–1.40 (m, 8 H, remaining aliphatic); UV λ_{max} (EtOH) 244 nm (ε 11100). Anal. (C₁₄H₁₇N·HCl) C, H, N, Cl.

***exo*-5,6-Dihydro-7-phenyl-1,5,9-methano-9H-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 (CDCl₃) δ 6.48 (d, *J* = 7 Hz, 1 H, CH=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 Et₂O (3 × 100 mL). The aqueous solution was basified with 2 M NaOH and extracted with Et₂O (3 × 100 mL). The extracts were combined, dried (Na₂SO₄), and evaporated, and the residue was distilled to give the allylamines 15 as colorless oils (Table I). Reactions with Me₂NH and EtNH₂ 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 N₂. The mixture was heated under reflux for 24 h and then cooled. Saturated NH₄Cl (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 (Na₂SO₄), 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).** Br₂ (11.8 g, 0.067 mol) was added dropwise to a solution of 5 (12.5 g, 0.067 mol) in CCl₄ (100 mL) at 0 °C under N₂. 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 Et₂O (3 × 50 mL), basified with 2 M NaOH, and extracted with Et₂O (3 × 50 mL). The extracts were combined, dried (MgSO₄), and evaporated, and the residue was distilled *in vacuo* to give the allylamines 16.

Method C. Methylation of Allylamines 16 (R₁ = H). A solution of 16 (R₁ = H) (0.003 mol) in 40% aqueous HCHO (3 mL) and 98% HCO₂H (3 mL) was heated at 100 °C for 4 h. The solution was cooled, poured into 2 M NaOH (30 mL), and extracted with Et₂O (3 × 50 mL). The extracts were combined, dried (Na₂SO₄), and evaporated, and the residue was distilled *in vacuo* to give the allylamines 16 (R₁ = 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 NaN₃ (0.75 g, 0.015 mol) in dry DMF (20 mL) was stirred at room temperature for 1.5 h and then poured into H₂O (300 mL). The solution was extracted with Et₂O (3 × 150 mL), and the extracts were combined, washed with H₂O (5 × 100 mL), dried (MgSO₄), 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 (CDCl₃) δ 7.30 (m, 5 H, aromatic), 6.48 (d, *J* = 6 Hz, CH=CPh, *exo* isomer), 6.28 (d, *J* = 6 Hz, CH=CPh, *endo* isomer), 4.88 (d, *J* = 5 Hz, CHN₃, *endo* isomer), 4.00 (d, *J* = 3 Hz, CHN₃, *exo* isomer), 2.70 (m, 2 H, 2 CH), 2.20–1.20 (m, 6 H, 3 CH₂); IR (liquid film) ν_{max} 2190 (N₃) 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 Et₂O (70 mL) was added dropwise over 1 h to a stirred suspension of LiAlH₄ (5.5 g, 0.14 mol) in dry Et₂O (200 mL) at 0 °C under N₂. 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 (Na₂SO₄) and then treated with 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 (CDCl₃), 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, CH=CPh) and 4.23 (d, *J* = 5 Hz, CHNH₂).

***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% HCO₂H (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 Et₂O (3 × 200 mL), and the extracts were combined, dried (Na₂SO₄), 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 K₂CO₃. The product was extracted with EtOAc (3 × 150 mL), and the extracts were combined, dried (Na₂SO₄), 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; ¹H NMR (D₂O) δ 7.40 (m, 5 H, aromatic), 6.46 (d, *J* = 7 Hz, 1 H, CH=CPh), 5.00 (d, *J* = 4.5 Hz, 1 H, CHNMe₂), 6.3 (s, 2 H, maleic acid), 2.97 (br s, 1 H, =CHCH<), 2.70 (s, 6 H, NMe₂), 2.68 (br s, 1 H, Me₂NCCCH<), 2.10-1.70 (m, 6 H, remaining CH₂); UV λ_{max} (EtOH) 236 nm (ε 13 300). Anal. (C₁₆H₂₁N₂C₄H₄O₄) C, H, N: calcd, 4.1; found, 5.0. MS Calcd for C₁₆H₂₁N₂, 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 Carboxylalkyl Inhibitors of Brain Enkephalinase: Synthesis, Biological Activity, and Analgesic Properties

Marie-Claude Fournié-Zaluski,[†] Pierre Chaillet,[‡] Evelyne Soroca-Lucas,[†] Hélène Marçais-Collado,[†] Jean Costentin,[†] and Bernard P. Roques^{*†}

Departement de Chimie Organique, ERA 613 CNRS et SC 21 INSERM, U.E.R. des Sciences Pharmaceutiques et Biologiques, 75006 Paris, France, and Laboratoire de Pharmacodynamie, U.E.R. de Médecine et Pharmacie, Université de Rouen, 76800 Saint Etienne du Rouvray, France. Received May 28, 1982

New carboxylalkyl compounds derived from Phe-Leu and Phe-Ala were synthesized and checked as inhibitors of "enkephalinase", a metalloendopeptidase cleaving the Gly³-Phe⁴ 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*₁ ≈ 0.5 μM), competitive and selective inhibitors of the enkephalin-degrading enzyme. The most interesting compound, *N*-[(*R,S*)-2-carboxy-3-phenylpropanoyl]-L-leucine (**3**, *K*₁ = 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-Ala²-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 ED₅₀ 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 aminopeptidases⁵⁻⁸ and the two peptidyl dipeptide hydrolases, "enkephalinase"⁹⁻¹³ and angiotensin-converting enzyme (ACE),¹⁴ are able to degrade enkephalins by cleavage of the Gly³-Phe⁴ 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 S₁' subsite, specific

for aromatic residues, and a lipophilic S₂' subsite without a marked selectivity except its aversion for proline and

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[†] U.E.R. des Sciences Pharmaceutiques et Biologiques.

[‡] U.E.R. de Médecine et Pharmacie.