(Na_2SO_4) and evaporated under reduced pressure to leave a light yellow mobile liquid. This was treated with 3 mL of phenyl isocyanate and was permitted to stand overnight at room temperature. Methanol (25 mL) was cautiously added and the resulting mixture was heated on a steam bath for 0.25 h; then it was evaporated under reduced pressure. The residue was taken up in benzene and this solution was extracted repeatedly with 2.5 N HCl. The pooled HCl extracts were washed with Et_2O, then excess 50% KOH was added, and the resulting mixture was extracted repeatedly with Et_2O. The pooled, dried (Na_2SO_4) ethereal extracts were evaporated under reduced pressure to afford an oily residue which was distilled. See Table II.

Ether Cleavage Reactions. The distilled amine (0.017 mol) was heated with 50 mL of 48% HBr under N_2 for 3 h. Volatiles were removed under reduced pressure, and the residue was recrystallized. See Table II.

Acknowledgment. This investigation was supported in part by Grant GM-22365, National Institute of General Medical Sciences, and in part by the Medical Research Council of the United Kingdom. Miss M. Y. Green gave excellent technical assistance throughout the behavioral studies.

References and Notes

(1) M. Ilhan, J. P. Long, and J. G. Cannon, *Arch. Int. Pharmacodyn. Ther.*, **212**, 247 (1974).
(2) M. Ilhan, J. P. Long, and J. G. Cannon, *Eur. J. Pharmacol.*, **33**, 13 (1975).
(3) J. M. Kitzen, J. P. Long, and J. G. Cannon, *Eur. J. Pharmacol.*, **38**, 365 (1976).
(4) J. Z. Ginos, G. C. Cotzias, E. Tolosa, L. C. Tang, and A. LoMonte, *J. Med. Chem.*, **18**, 1194 (1975).
(5) B. Costall, R. J. Naylor, and J. L. Neumeyer, *Eur. J. Pharmacol.*, **31**, 1 (1975).
(6) J. D. McDermed, G. M. McKenzie, and A. P. Phillips, *J. Med. Chem.*, **18**, 362 (1975).
(7) B. Costall, R. J. Naylor, J. G. Cannon, and T. Lee, *Eur. J. Pharmacol.*, **41**, 307 (1977).
(8) A. O. Elkhawad and G. N. Woodruff, *Br. J. Pharmacol.*, **54**, 107 (1975).
(9) M. K. Menon, W. G. Clark, and J. G. Cannon, *J. Pharm. Pharmacol.*, **28**, 778 (1976).
(10) P. Marchini, G. Liso, A. Reho, F. Liberatore, and F. M. Moracci, *J. Org. Chem.*, **40**, 3453 (1975).
(11) H. C. Cheng and J. P. Long, *Eur. J. Pharmacol.*, **26**, 313 (1974).
(12) M. Ilhan and J. P. Long, *Arch. Int. Pharmacodyn. Ther.*, **216**, 4 (1975).
(13) U. Ungerstedt, *Acta Physiol. Scand., Suppl.*, **367**, 69 (1971).
(14) P. H. Kelly and K. E. Moore, *Nature (London)*, **263**, 695 (1976).
(15) J. G. Cannon, T. Lee, H. D. Goldman, B. Costall, and R. J. Naylor, *J. Med. Chem.*, **20**, 1111 (1977).
(16) B. Costall and R. J. Naylor in "Cocaine and Other Stimulants", E. H. Ellinwood and M. M. Kilbey, Ed., Plenum Press, New York, N.Y., 1976, pp 47–76.
(17) A. J. J. Pijnenburg and J. M. Van Rossum, *J. Pharm. Pharmacol.*, **25**, 1003 (1973).
(18) B. Costall, R. J. Naylor, J. G. Cannon, and T. Lee, *J. Pharm. Pharmacol.*, **29**, 337 (1977).
(19) J. De Groot, *Verh. K. Ned. Akad. Wet.*, **52**, 14 (1959).
(20) B. Costall, R. J. Naylor, and C. J. Pycock, *J. Pharm. Pharmacol.*, **27**, 943 (1975).
(21) R. J. Borgman, J. J. McPhillips, R. E. Stitzel, and I. J. Goodman, *J. Med. Chem.*, **16**, 630 (1973).

Acetylenics. 2. Synthesis and Pharmacology of Certain *N,N*-Dialkyl-3-phenylpropyn-2-amines. Some Analogues with Tryptamine-Like Behavioral Effects in Mice[1]

Madan M. Kwatra, David Z. Simon,* Romano L. Salvador, and Paul D. Cooper

Department of Medicinal Chemistry, Faculty of Pharmacy, University of Montreal, Montreal, Canada.
Received March 3, 1977

A number of *N,N*-dialkyl-3-phenylpropyn-2-amines **7** have been prepared and tested for their biological action. Certain analogues show tryptamine-like behavioral effects in mice. The tryptamine-like activity of these compounds appears to be controlled by their lipophilicity. These compounds show only weak inhibition of rat liver monoamine oxidase. Although these compounds exhibit tryptamine-like action, experiments seem to indicate that there is no interaction with the tryptamine receptors.

Some time ago we reported the synthesis of some 3-phenylpropyn-2-amines.[2a] Preliminary pharmacological studies revealed that these compounds possessed some monoamine oxidase (MAO) inhibitory, anorexigenic, and blood lipid lowering activity.[2b] To study these compounds in greater detail, we undertook the synthesis of a number of their analogues. This paper reports the synthesis and pharmacology of certain *N,N*-dialkyl-3-phenylpropyn-2-amines **7**.

Compounds **7** were tested in vitro for their anti-MAO action and were subjected to a general pharmacological screening in mice. Tryptamine-like behavioral effects, not hitherto seen with these types of compounds,[3] were observed with some of the analogues.

Chemistry. Scheme I shows the synthetic routes used for the preparation of compounds **7**. Although all the compounds **7** (Table I) could be prepared by the Mannich reaction[4] (method A), the synthesis via the alcohol **5** (method B) was used to overcome the requirement of difficultly available substituted phenylacetylenes. In method B, the coupling of iodobenzenes with copper(I) acetylenides to prepare the alcohols **5** was according to the method of Atkinson et al.[5] The coupling reaction using the copper(I) acetylenide derived from the unprotected propargyl alcohol did not work and the unreacted acetylenide was recovered. This unreacted copper(I) acetylenide, probably because of long reflux in pyridine, was found to be highly explosive. Therefore the copper(I) acetylenide derived from the protected propargyl alcohol was used. In this way the coupling reaction proceeded smoothly giving a good yield of compound **4**.

Biological Testing and Results. In Vitro MAO Inhibition. All the final compounds (**7a–j**) were tested for their inhibitory action on rat liver MAO using kynuramine (10^{-4} M) as the substrate.[6] The MAO was solubilized[7] with Triton X-100. The activity was measured by following the increase in absorbance at 316 nm, due to the formation of 4-hydroxyquinoline, and not by following the decrease in absorbance, due to the disappearance of kynuramine, at 360 nm. It was found that, at a given

0022-2623/78/1821-0253$01.00/0

Table I. Percent Yield and Physical Data of Various Compounds 7

Compd	X	R	Bp (mm), °C, free base	Yield, %	Mp, °C, HCl salt[a]	Method	Mol formula	Analyses
7a	H	CH_3			160-161			[b]
7b	m-CF_3	CH_3	62-64 (0.2)	80	180-182	B	$C_{12}H_{13}NF_3Cl$	C, H, N, F
7c	H	C_2H_5			138-140			[b]
7d	m-CF_3	C_2H_5	66-68 (0.2)	77	154-156	B	$C_{14}H_{17}NF_3Cl$	C, H, N, F
7e	H	n-Pr	96-97 (0.35)	79	152-153	A	$C_{15}H_{22}NCl$	C, H, N
7f	m-CF_3	n-Pr	92-94 (0.25)	74	140-142	B	$C_{16}H_{21}NF_3Cl$	C, H, N; F[c]
7g	p-Cl	n-Pr	104-106 (0.2)	60	141-142	A	$C_{15}H_{21}NCl_2$	C, H, N, Cl
7h	H	i-Pr	84-86 (0.2)	74	131-132	A	$C_{15}H_{22}NCl$	C, H, N
7i	m-CF_3	i-Pr	82-84 (0.2)	70	136-137	A	$C_{16}H_{21}NF_3Cl$	C, H, N, F
7j	p-Cl	i-Pr	98-100 (0.2)	65	129-130	A	$C_{15}H_{21}NCl_2$	C, H, N, Cl

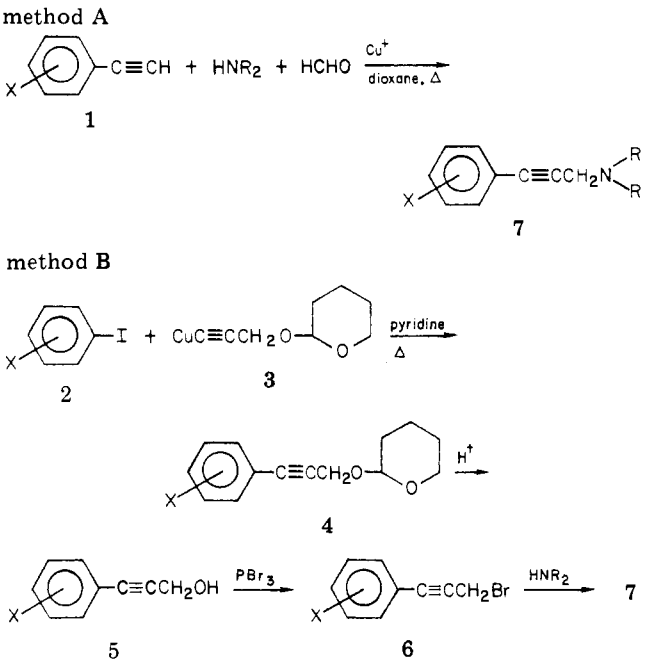
[a] Recrystallized from EtOH-Et_2O. [b] Prepared as reported previously.[2a] [c] F: calcd, 17.82; found, 17.26.

Table II. Monoamine Oxidase (Rat Liver) Inhibitory Activity of Compounds 7 (Kynuramine as a Substrate)

Compd	% inhibn (±10%) 10^{-4} mol/L	% inhibn (±10%) 10^{-5} mol/L
7a	50	10
7b	66	22
7c	39	10
7d	45	10
7e	12	0
7f	12	0
7g	12	0
7h	10	0
7i	17	0
7j	17	0
Pargyline[a]	45	
Pargyline[b]	78	

[a] At 3.6×10^{-6} M and without any preincubation. [b] At the same concentration but with a 10-min preincubation with the enzyme.

Scheme I



enzyme concentration, the increase in absorbance at 316 nm is greater than the decrease in absorbance at 360 nm. The compounds were tested at 10^{-4} and 10^{-5} M concentrations, with and without preincubation with the enzyme. Preincubation with the enzyme does not result in greater inhibition. Table II lists the percent inhibition.

Pharmacology. All the compounds were tested for gross behavioral effects in mice at an initial dose of 50 mg/kg ip. Table III summarizes these results along with approximate LD_{50} values. Compounds **7a** and **7c** do not show any observable effects at this dose and at higher doses only toxic symptoms (intense tonic convulsions of the forelimbs) can be seen. Compound **7b** is also inactive at this dose level. However, in higher doses it causes decreased motor activity of short duration (~10 min). Compound **7d**, on the other hand, shows quite pronounced activity. It causes a decrease in motor activity and hind limb extension lasting about 10–15 min, followed by a 5–10-min period of clonic seizures of the hind quarters. The total action lasts about 45 min.

The effects observed with compound **7e**, the di-*n*-propyl analogue, are also quite pronounced. However, the action of this compound differs from that of compound **7d** in that the animals immediately show pronounced (more intense than that induced by compound **7d**) and frequent (5–6 per min) clonic seizures of the hind quarters. Except for these seizures the animals remain motionless. The clonic seizures decrease after 10 min and are infrequent after 15–20

Table III. General Pharmacological Screening of Compounds 7. Overt Behavioral Effects in Mice

Compd	LD_{50}, mg/kg ip	Min dose at which effects obsd, mg/kg ip	Mouse symptomatology at 50 mg/kg ip
7a	125	100	No observable effects
7b	200	100	No observable effects
7c	125	100	No observable effects
7d	200	>25	Decreased motor activity, hind limb extension lasting 10–15 min followed by clonic seizures of the hind quarters
7e	175	<25	Clonic seizures of the hind quarters lasting 15-20 min, decreased motor activity lasting 1 h
7f	200	<25	Same as 7e except the clonic seizures last 20-25 min
7g	275	<25	Same as 7f
7h	150	>25	Decreased motor activity, some clonic seizures
7i	200	>25	Same as 7f except with shorter duration of the clonic seizures
7j	225	>25	Same as 7i
Tryptamine		<25	Clonic seizures of the hind quarters lasting 10-15 min, decreased motor activity lasting 25-30 min

min. The period of decreased motor activity lasts about 1 h. Compounds **7f** and **7g**, the *m*-CF_3 and *p*-Cl analogues of compound **7e**, show similar but slightly more pronounced effects (Table III). The diisopropyl analogues (**7h–j**) show similar but less pronounced effects than their di-*n*-propyl counterparts (Table III). Of these compounds **7h** shows the least activity. All of compounds **7** show stimulant action (increased motor activity and tonic convulsions) at doses approaching their LD_{50} values.

In an attempt to relate these observed effects to those of known pharmacological agents, a number of CNS active compounds were evaluated for their behavioral effects in mice. And these were the following: amphetamine, tremorine, tryptamine, mescaline, LSD, methysergide, hexobarbital, perphenazine, amitryptyline, metrazol, tranylcypromine, and pargyline.

It was found, by an instance of serendipity, that tryptamine, when given to mice at a dose of 50 mg/kg ip, produces behavioral effects that are similar to that described for compound **7e**. The only obvious difference is that tryptamine has a shorter duration of action. This is presumably due to its inactivation by MAO. Some resemblance to the action of methysergide, mescaline, and LSD is also seen.

Having noted the similarity between tryptamine and these compounds, the question arose as to their possible mechanism of action. Are these compounds acting at tryptamine receptors or are similar effects being produced by some other mechanism?

Some compounds of the original series showed MAOI activity.[2] These new compounds, therefore, were evaluated for MAOI activity (Table II). It is interesting to note that the compounds showing the more pronounced tryptamine-like activities, i.e., the di-*n*-propyl analogues, have negligible MAOI activity at 10^{-4} M and no inhibitory action at 10^{-5} M concentration. It appears, in fact, that there is little to no relationship between the tryptamine-like activity of some of these new compounds and their ability to inhibit MAO.

To ascertain whether the tryptamine-like activity is due to interaction with tryptamine receptors, experiments with tryptamine antagonists were undertaken. Compound **7e** was selected for these experiments since the di-*n*-propyl analogues show the more pronounced activity and, among these, this represents the parent compound. Since compound **7e** and its analogues cause a decrease in motor activity, the effect of compound **7e** on the hexobarbital sleeping time in mice was also studied.

Interaction of Compound 7e and Tryptamine with Tryptamine Antagonists. Although tryptamine and 5-hydroxytryptamine (5-HT) might act on different receptors,[8,9] the action of these two compounds is antagonized by the same classes of antagonists.[10,11] To study the antagonism of the behavioral effects of tryptamine and compound **7e**, we have used the following tryptamine–5-HT antagonists: 2-bromo-*d*-lysergic acid diethylamide (BOL), 1-methyl-*d*-lysergic acid butanolamide (methysergide), and cyproheptadine. These agents have been used as tryptamine antagonists in various studies. For example, BOL has been used to antagonize the behavioral effects of tryptamine in rats.[12] Methylsergide and BOL have been used as tryptamine antagonists to study the involvement of tryptaminergic mechanism in behavioral inhibition.[13] Cyproheptadine has been shown to antagonize the flexor reflex enhancement caused by tryptamine in chronic spinal dog.[14] However, as far as we know, methysergide and cyproheptadine have not been used to study the antagonism of the behavioral effects of tryptamine.

Table IV. Effect of Compound 7e on the Hexobarbital Sleeping Time in Mice

Pretreatment	Dose, mg/kg ip	Sleeping time in min ± SD	p^a
Saline[b]		24.3 ± 7.8	
7e[b]	26	41.3 ± 9.2	<0.005
Saline[c]		30.4 ± 2.4	
7e[c]	48	71.0 ± 16.0	<0.0005

[a] From *t* test. [b] With 61 mg/kg ip of hexobarbital. [c] With 67 mg/kg ip of hexobarbital.

BOL. When tryptamine (25 mg/kg ip) is given to mice pretreated with BOL (2 mg/kg ip), its effects are completely antagonized. However, when compound **7e** (25 mg/kg ip) is given to mice pretreated with BOL (2 mg/kg ip), its effects are not antagonized. Instead, an increase in the period of clonic seizures of the hind quarters, produced by compound **7e**, is observed.

Methysergide. In methysergide (10 mg/kg ip) treated mice, the behavioral effects of tryptamine (25 mg/kg ip) are not antagonized. A higher dose (20 mg/kg ip) and a lower dose (5 mg/kg ip) of methysergide is also ineffective in antagonizing the behavioral effects of tryptamine (25 mg/kg ip). Similarly, no antagonism to the action of compound **7e** (25 mg/kg ip) is shown by methysergide.

Cyproheptadine. In mice pretreated (10 min) with cyproheptadine (3 mg/kg ip), the effects of tryptamine (25 mg/kg ip) are not antagonized. Instead, an increase in the intensity of clonic seizures of the hind quarters is observed. Similar results are obtained with compound **7e**. When tryptamine (25 mg/kg ip) or compound **7e** (25 mg/kg ip) is given 40 min after cyproheptadine (3 mg/kg ip), the period of clonic seizures is decreased but the animals become "flat" and show fasciculations of the hind quarters without any movements. These results seem to show that cyproheptadine potentiates, rather than antagonizes, the behavioral effects of tryptamine. Similarly, it potentiates the behavioral effects of compound **7e**.

Effect of Compound 7e on the Hexobarbital Sleeping Time in Mice. Table IV shows the data on hexobarbital sleeping time, with and without compound **7e**. The prolongation of hexobarbital sleeping time in mice by compound **7e** confirms a sedative component to the action of this compound. Although many drugs prolong the hexobarbital sleeping time, it might be relevant to mention that tryptamine has also been reported to prolong hexobarbital sleeping time in mice.[15]

Discussion

Since not all of compounds **7** show this tryptamine-like behavioral effects in mice (Table III), an attempt was made to explain this observation. Since the diethyl analogue **7d** and the diisopropyl analogues **7h–j**, in addition to the di-*n*-propyl analogues **7e–g**, show this activity, it is clear that this activity is not due, solely, to the nature of the *N,N*-dialkyl substituents. It seems, rather, to be a property of the parent structure, 3-phenylpropyn-2-amine. The fact that compounds **7a–c** (Table III) do not show this activity might be explained in terms of their lipophilicity. Table V lists the calculated log *P* values of the various compounds **7**. Since the diethyl analogue **7d** with a lipophilic substituent on the benzene ring is active and the diethyl analogue **7c** without any such group is inactive, it is suggestive that the inactivity of compounds **7a–c** is due to their lower log *P* values, at least to a first approximation.

Although the behavioral effects are clearly tryptamine-like, experiments with tryptamine antagonists such as BOL, cyproheptadine, and methysergide have failed to indicate that the action of **7e** is due to any interaction with

Table V. Calculated Log P Values of Compounds 7

Compd	Log P[a]	Compd	Log P[a]
7a	2.19[b]	7f	5.40
7b	3.40	7g	4.89
7c	3.19[c]	7h	3.79[d]
7d	4.40	7i	5.00
7e	4.19	7j	4.46

[a] Obtained by adding the π values of the substituents to the π value of the $C_6H_5C{\equiv}CCH_2N$ unit. A π value of 1.19 ± 0.13 is calculated for this unit from the experimentally determined log P values of four different 3-phenylpropyn-2-amines (ref 16). The following π values for these substituents were used: $\pi(CH_3) = 0.50$, $\pi(C_2H_5) = 1.00$, $\pi(n\text{-Pr}) = 1.50$, $\pi(i\text{-Pr}) = 1.30$ (ref 17). [b] Experimental log $P = 1.97$ (ref 16). Log P of this compound can also be calculated in the following manner: log P $[C_6H_5C{\equiv}CCH_2N(CH_3)_2] = \log P\,(C_6H_5C{\equiv}CH) + \pi(CH_2) + \pi[N(CH_3)_2] = 2.53 + 0.50 - 0.95 = 2.08$ (see ref 18), which is in good agreement with the experimental value and with the calculated value listed in the table. [c] Experimental log $P = 3.44$ (ref 16). [d] Compounds having a log P value lower than this do not show tryptamine-like behavioral effects.

the tryptamine receptors, and the mechanism of action is not clear. Nevertheless, there is a close structural similarity between tryptamine and the 3-phenylpropyn-2-amine moiety, in terms of the planarity of the indole ring and the phenylethynyl group, respectively. It has been reported[19,20] that the replacement of the indolic imino moiety of tryptamine or 5-HT by CH_2, O, or S does not change the relative intrinsic activity; it would appear that the π-electron cloud of the indole ring is the important factor for interaction with the receptor. One might speculate that the π-electron cloud of the phenylethynyl group plays a similar role. When the molecular models (Dreiding) of tryptamine and 3-phenylpropyn-2-amine are compared, it is found that they are superimposable.

Experimental Section

Infrared spectra were recorded on a Beckman IR-18A and ^1H NMR spectra on a Perkin-Elmer R-12B spectrometer. Elemental analyses were performed by Micro-Tech laboratories, Skokie, Ill. Unless otherwise indicated, the analyses were within ±0.4% of the calculated values. Melting and boiling points are uncorrected. The *m*-trifluoromethyl- and *p*-chlorophenylacetylenes 1 were prepared according to reported methods.[21] 3-Tetrahydropyranyloxyprop-1-yne [bp 64–66 °C (15 mm)] was prepared according to the method of Woods and Kramer.[22] Copper(I) 3-tetrahydropyranyloxyprop-1-ynide (3) was prepared in 80% yield according to the method of Owsley and Castro.[23] Compound 3 was well dried prior to use and its handling was found to be quite safe. The *m*-trifluoromethyliodobenzene 2 was prepared from the corresponding aniline by the Sandmeyer reaction [bp 74–76 °C (20 mm)] [lit.[24] 82–82.5 °C (25 mm)]. All other chemicals were purchased from commercial sources. The biological testing was done using the hydrochloride salts of compounds 7. The MAO activity was measured on a Beckman DB-G spectrometer equipped with a recorder. Centrifugations were carried out in Sorvall RC2-B centrifuge at 4 °C, 15000g for 20 min. Phosphate buffer (Na_2HPO_4–NaH_2PO_4, 0.1 M, pH 7.6) was used in the preparation and assays of MAO.

Synthesis. Method A. Mannich Reaction. A mixture of the appropriate phenylacetylene 1 (0.1 mol), secondary amine (0.11 mol), paraformaldehyde (3.6 g), and CuI (0.5 g) was taken up in dioxane (40 mL) and was allowed to reflux overnight. The reaction mixture was cooled and was taken up in Et_2O (200 mL), washed 3–4 times with water, and dried (Na_2SO_4), and Et_2O was removed. The resulting oil was distilled to afford the free base of compound 7 (Table I).

Method B. 3-Tetrahydropyranyloxy-1-(*m*-trifluoromethyl)phenylprop-1-yne (4).[5] Copper(I) acetylenide 3 (0.1 mol) and compound 2 (0.1 mol) were dissolved in dry pyridine (250 mL), and the mixture was refluxed under N_2 for 15 h. The reaction mixture was cooled and poured into water (500 mL). After stirring for a few minutes, the mixture was allowed to stand for 1–2 h. The upper greenish solution was decanted and the dark brown precipitate was thoroughly extracted with Et_2O. The Et_2O solution was washed with 2 N HCl, saturated $NaHCO_3$, and water and dried (Na_2SO_4). After removing Et_2O the resulting oil was distilled to afford compound 4: bp 110–112 °C (0.25 mm); yield 70%.

3-(*m*-Trifluoromethyl)phenylpropyn-2-ol (5). Compound 4 (0.05 mol) and *p*-toluenesulfonic acid (1 g) were dissolved in EtOH (50 mL), and the mixture was refluxed for 2–3 h. The reaction mixture was cooled and treated with anhydrous K_2CO_3 (2–3 g). After filtration, the EtOH was removed in vacuo and the residue was taken up in Et_2O, washed with water, and dried (Na_2SO_4). After removing Et_2O, the product was distilled to give the alcohol 5 in almost quantitative yield: bp 73–74 °C (0.2 mm); n^{22}_D 1.507. Anal. ($C_{10}H_7OF_3$) C, H; F: calcd, 28.47; found, 27.79.

3-Bromo-1-(*m*-trifluoromethyl)phenylprop-1-yne (6).[25] Alcohol 5 (0.05 mol) and dry pyridine (1 mL) were dissolved in dry Et_2O (20 mL) and cooled to 0 °C. PBr_3 (0.025 mol) in dry Et_2O (20 mL) was added drop by drop with stirring. The reaction mixture was refluxed for 3 h. After cooling to 0 °C, the excess PBr_3 was destroyed by adding crushed ice. The Et_2O layer was separated and the aqueous phase extracted twice with Et_2O. The Et_2O extracts were combined and washed with saturated $NaHCO_3$, saturated NaCl, and water. After drying (Na_2SO_4), the Et_2O was removed and the product distilled: bp 60–61 °C (0.2 mm); yield 77%; n^{22}_D 1.536. Anal. Calcd for $C_{10}H_6F_3Br$: C, 45.66; H, 2.30; F, 21.67. Found: C, 45.05; H, 2.45; F, 21.17.

***N,N*-Dialkyl-3-(*m*-trifluoromethyl)phenylpropyn-2-amine (7).** Compound 6 (0.05 mol) was added slowly with stirring to the appropriate secondary amine (0.5 mol) and was allowed to stir for 2–3 h. To the reaction mixture was added an excess of Et_2O and the precipitate filtered off. The filtrate was washed with water and dried (Na_2SO_4), and the solvent was removed to give an oil which was distilled to obtain compound 7 (Table I).

Isolation of Rat Liver Mitochondria. Male Wistar rats (150–200 g) were starved for 24 h and killed by decapitation, and the livers were removed. The mitochondria were isolated according to the method of Johnson and Lardy[26] except that to the isotonic sucrose solution (0.25 M) was added 0.001 M EDTA and the solution was adjusted to pH 7.0 with 10% NaOH. For the isolation of mitochondria, 7–8 g of liver tissue was used at a time.

Solubilization of Mitochondria with Triton X-100. The mitochondrial pellet was washed twice with phosphate buffer (20 mL). The pellet was taken up in 18–20 mL of the buffer containing 1% Triton X-100 and was stirred occasionally for 90 min. During this period, the preparation was kept in an ice bath. The preparation was centrifuged and the clear supernatant was used as the MAO preparation.

MAO Activity. The activity measurements were done at 30 °C and at pH 7.6. The reaction mixture had a volume of 3.0 mL made up of the following in the case of control activity: 0.3 mL of 10^{-3} M kynuramine dihydrobromide, 2.6 mL of the buffer, and 0.1 mL of MAO preparation. In inhibition experiments, it contained 0.3 mL of the test compound, 2.3 mL of the buffer, and the same amount of kynuramine and MAO as the control. In each case the reaction was started by adding the enzyme solution. The change in absorbance was read against a blank containing all the reagents except the substrate. Initial rates, as change in absorbance per minute, with and without the test compound were measured.

Pharmacology. Male albino Swiss mice (15–20 g) were used and in all the experiments described below, the animals were kept individually.

Hexobarbital Sleeping Time in Mice. Twelve mice of similar weights to ±1 g were used. Saline was given to six mice and another six mice received compound 7e (26 mg/kg ip). After 5 min, hexobarbital (61 mg/kg ip) was given to all the animals. The time in minutes for the loss and subsequent recovery of the righting reflex for the two groups was recorded. Similar experiments were done using a 48 mg/kg ip dose of compound 7e and in this case the dose of hexobarbital used was 67 mg/kg ip.

Interaction of Compound 7e and Tryptamine with Tryptamine Antagonists. In all experiments described below, two control groups of four to six mice were also included. One

control group received the antagonists followed, after an appropriate time, by saline. The other control group received saline followed, after an appropriate time, by tryptamine or compound **7e**.

BOL. Six mice were treated with BOL (2 mg/kg ip). This dose of BOL shows no behavioral effects. After 20 min, the animals were given 25 mg/kg ip of tryptamine. Similar experiments were done with compound **7e** (25 mg/kg ip).

Methysergide. Six mice were treated with methysergide (10 mg/kg ip). At this dose of methysergide, the animals show a decrease in motor activity and fasciculations of the hind quarters. Sometimes these fasciculations are intense and resemble the clonic seizures shown by tryptamine and compound **7e**. When the animals appeared normal (40 min), 25 mg/kg ip of tryptamine was given. Similar experiments were done with compound **7e**. The interaction of tryptamine and compound **7e** was also studied using 5 and 20 mg/kg ip doses of methysergide.

Cyproheptadine. Six mice were treated with cyproheptadine (3 mg/kg ip). The behavioral effects observed at this dose of cyproheptadine are increased exploration and occasional tremors of hind legs. After 10 min, tryptamine (25 mg/kg ip) or compound **7e** (25 mg/kg ip) was given. In another experiment, the animals were given tryptamine or compound **7e** 40 min after cyproheptadine.

Acute Toxicity in Mice. The compounds were tested at 25, 50, 100, 200, and 300 mg/kg ip doses, four mice being used per dose. Saline was used as the vehicle. The dose at which two of the animals died in a 24-h period was taken as the approximate LD_{50}. If at a given dose only one or three of the animals died, then the LD_{50} was calculated by adding or subtracting, respectively, 25 mg/kg from this dose.

Drugs and Their Source. Pargyline hydrochloride [prepared from *N*-methylbenzylamine and propargyl bromide, mp 155 °C (lit.[27] 154–155 °C)], BOL tartrate (Department of Health & Welfare, Canada), methysergide bimaleate (Sandoz, Montreal), cyproheptadine hydrochloride (Merck, Montreal), and tryptamine hydrochloride (Sigma Chemical Co., St. Louis, Mo.) were used.

References and Notes

(1) Taken in part from the Ph.D. thesis of M. M. Kwatra.
(2) (a) D. Z.. Simon, R. L. Salvador, and G. Champagne, *J. Med. Chem.*, **13**, 1249 (1970); (b) unpublished data, studies done by Ayerst Laboratories, Montreal, Canada.
(3) K. E. Schulte, *Chim. Ther.*, **4**, 496 (1969).
(4) M. Tramontini, *Synthesis*, 703 (1973).
(5) R. E. Atkinson, R. F. Curtis, D. M. Jones, and J. A. Taylor, *J. Chem. Soc. C*, 2173 (1969).
(6) H. Weissbach, T. E. Smith, J. W. Daly, B. Witkop, and S. Udenfriend, *J. Biol. Chem.*, **235**, 1160 (1960).
(7) S. Nara, B. Gomes, and K. T. Yasunobu, *J. Biol. Chem.*, **241**, 2774 (1966).
(8) J. C. Winter and P. K. Gessner, *J. Pharmacol. Exp. Ther.*, **162**, 286 (1968).
(9) D. W. Wooly and E. Shaw, *J. Pharmacol. Exp. Ther.*, **121**, 13 (1957).
(10) J. R. Vane, H. O. J. Collier, S. J. Corne, E. Marley, and P. B. Bradley, *Nature (London)*, **191**, 1068 (1961).
(11) A. L. Frankhuijzen and I. L. Bonta, *Eur. J. Pharmacol.*, **26**, 220 (1974).
(12) D. H. Tedeschi, R. E. Tedeschi, and E. J. Fellows, *J. Pharmacol. Exp. Ther.*, **126**, 223 (1959).
(13) F. G. Graeff, *J. Pharmacol. Exp. Ther.*, **189**, 344 (1974).
(14) W. R. Martin and C. G. Eades, *Psychopharmacologia*, **17**, 242 (1970).
(15) P. Mantegazzini in "Handbook of Experimental Pharmacology", V. Erspamer, Ed., Vol. XIX, Springer-Verlag, Berlin, 1966, p 441.
(16) R. L. Salvador, unpublished data.
(17) J. G. Topliss, *J. Med. Chem.*, **15**, 1006 (1972).
(18) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
(19) R. M. Pinder, D. M. Green, and P. B. J. Thompson, *J. Med. Chem.*, **14**, 626 (1971).
(20) J. C. Winter, P. K. Gessner, and D. D. Godse, *J. Med. Chem.*, **10**, 856 (1967).
(21) I. J. Solomon and R. Filler, *J. Am. Chem. Soc.*, **85**, 3492 (1963); M. M. Otto, *ibid.*, **56**, 1393 (1934); C. D. Cook and S. S. Danyluk, *Tetrahedron*, **19**, 177 (1963).
(22) G. F. Woods and D. N. Kramer, *J. Am. Chem. Soc.*, **69**, 2246 (1947).
(23) D. C. Owsley and C. E.. Castro, *Org. Synth.*, **52**, 128 (1972).
(24) G. C. Finger and M. L. Kanowski, *Trans. Ill. State Acad. Sci.*, **37**, 66 (1944); *Chem. Abstr.*, **39**, 1146 (1945).
(25) R. Mantione, *Bull. Soc. Chim. Fr.*, 4514 (1969).
(26) D. Johnson and H. Lardy, *Methods Enzymol.*, **10**, 94 (1967).
(27) "The Merck Index", 8th ed, Merck & Co., Rahway, N.J., 1968, p 784.

Analgesic and Tranquilizing Activity of 5,8-Disubstituted 2-Aminomethyl-3,4-dihydronaphthalenes

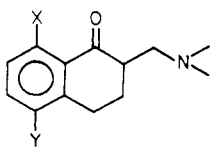
Willard M. Welch,* J. J. Plattner, Wilford P. Stratten, and C. A. Harbert

Pfizer Inc., Medical Research Laboratories, Groton, Connecticut 06340.

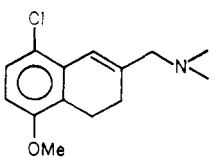
Received August 22, 1977

Interesting analgesic activity approaching that of meperidine and codeine was observed in standard animal models for 8-chloro-3,4-dihydro-5-methoxy-2-pyrrolidinomethylnaphthalene (compound **7**). This compound was orally effective and its analgesic activity was not reversed by the opiate antagonist, naloxone. A limited number of other 2-aminomethyl analogues displayed activity in neuroleptic screens.

An investigation of the structural requirements for analgesic and tranquilizing activity in a series of 5,8-disubstituted 1-tetralone Mannich bases I has recently been



I



II

reported.[1] In an extension of this work we have found that the related 2-aminomethyl-3,4-dihydronaphthalene compounds II also exhibit interesting CNS activity. In this paper we wish to describe the synthesis and biological activity of a series of 2-aminomethyl-8-chloro-3,4-dihydro-5-methoxynaphthalenes together with a probe into the effect of substitution on the aromatic ring in the pyrrolidinomethyl series.

Chemistry. The 2-aminomethyl-3,4-dihydronaphthalene derivatives described in this paper were prepared by two main routes depending in part upon the nature of the desired amine substituent. The first route (Scheme I) was employed in cases where the amine substituent was not sensitive to hydride reducing agents. As indicated in Scheme I, the ethyl ester of 4-(2-methoxy-5-chlorophenyl)butyric acid[2] (III) was converted to the unstable hydroxymethylene derivative IV by means of sodium

0022-2623/78/1821-0257$01.00/0