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Synthesis and Antidepressant Activity of 5-Phenyl-2-(2-propynylamino)-2-oxazolin-4-one and Derivatives

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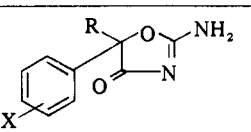
5-Phenyl-2-(2-propynylamino)-2-oxazolin-4-one and derivatives were synthesized by heating 2-amino-5-phenyl-2-oxazolin-4-one and its derivatives with 2-propynylamine in ethanol. 2-[(1,1-Dialkyl-2-propynyl)amino]-5-phenyl-2-oxazolin-4-ones were obtained by cyclization of 1-(α-chlorophenylacetyl)-3-(1,1-dialkyl-2-propynyl)ureas with sodium ethoxide in ethanol. These compounds were evaluated for antidepressant activity by the dopa response potentiation test.

2-Amino-5-phenyl-2-oxazolin-4-one was synthesized by Traube and Ascher in 1913.[1] Because of its central stimulant property,[2] it has been used as a mild stimulant,[3] antidepressant,[4] and antifatigue agent.[5] Many of its derivatives and analogs had been synthesized. The 2-amino group was replaced by monoalkylamino,[6] dialkylamino,[7] allylamino,[7] cycloalkylamino,[8] phenylamino,[7] phenylalkylamino,[6] and 5,-6-membered nitrogen heterocycles such as pyrrolidine, piperidine, morpholine, and piperazine.[9,10] The pharmacologic spectrum of 2-dimethylamino-5-phenyl-2-oxazolin-4-one (thozalinone) was found to lie between amphetamine and imipramine and is a central excitant with anorexigenic properties.[11] 2-Cyclopropylamino-5-phenyl-2-oxazolin-4-one is an antifatigue agent.[12] 2-Amino-5-phenyl-2-oxazolin-4-one (pemoline) with magnesium hydroxide was reported to be a unique type of stimulant.[13] Recently the spiral analogs of 2-amino-5-phenyl-2-oxazolin-4-one in which the carbon atom to which the phenyl group is attached is part of a spirane system were synthesized and were found to be less active in increasing spontaneous activity in mice than pemoline.[14]

Since the report of *N*-benzyl-*N*-methyl-2-propynylamine (pargyline) as a nonhydrazine MAO inhibitor,[15] used for treatment of hypertension and depression,[16] there have been several reports of incorporating the 2-propynylamino group in various structures to produce enhanced MAO inhibitors,[17,18] antidepressant activity,[19,20] and anticonvulsant activity.[21] The 2-propynylamino group appears to contribute its unique pharmacological properties to the molecules. Therefore, it seemed desirable to replace the amino group in 2-amino-5-phenyl-2-oxazolin-4-one by 2-propynylamino group and its homologs and to evaluate their antidepressant activity. Recently a review article of synthetic and natural acetylenic compounds as medicines appeared.[22]

Chemistry. Several new 2-amino-5-aryl-2-oxazolin-4-ones (Table I) were obtained by reaction of the appropriately substituted ethyl mandelates with guanidine in EtOH. 5-Phenyl-2-(2-propynylamino)-2-oxazolin-4-one and derivatives (**3a–l**)(Table II) were prepared by refluxing 5-substituted 2-amino-2-oxazolin-4-ones (**1a-k**) with 2 equiv of 2-propynylamine (**2a**) or 1-methyl-2-propynylamine (**2b**) in EtOH (method A, Scheme I). Attempts to obtain 2-[(1,1-dimethyl-2-propynyl)amino]-5-phenyl-2-oxazolin-4-one (**7a**) by the above method were unsuccessful. 2-[(1,1-Dialkyl-2-propynyl)amino]-5-phenyl-2-oxazolin-4-ones (**7a–c**) (Table III) were prepared by method B, Scheme I. (1,-1-Dialkyl-2-propynyl)ureas (**5a–c**) were obtained by reaction of (1,1-dialkyl-2-propynyl)amines·HCl with aqueous KCNO. Treatment of **5a-c** with α-chlorophenylacetyl chloride in

Table I. 2-Amino-5-aryl-2-oxazolin-4-ones



Compd[a]	X	R	Mp, °C	Yield, %	Crystn solvent	Formula[b]
1d	3-CF_3	H	223–224	23	EtOH	$C_{10}H_7F_3N_2O_2$
1e	2-CH_3	H	212–222	44	EtOH	$C_{10}H_{10}N_2O_2$
1f	4-$CH(CH_3)_2$	H	227–229	52	EtOH	$C_{12}H_{14}N_2O_2$
1h	4-OC_5H_{11}	H	232–234	30	EtOH-H_2O	$C_{14}H_{18}N_2O_3$
1i	3,4,5-$(OCH_3)_3$	H	224–225	50	EtOH	$C_{12}H_{14}N_2O_5$

[a]Compd 1a (X = H; R = H), mp 245–247°, lit.[7] mp 254–256°; 1b (X = 4-Cl; R = H), mp 275–276°, lit.[7] mp 268–269°; 1c (X = 2-F; R = H), mp 232–233°, lit.[7] mp 235–237°; 1g (X = 4-OCH_3; R = H), mp 236–237°, lit.[25] mp 278–279°; 1j (X = H; R = CH_3), mp 202–204°, lit[7] mp 206–207°; 1k (X = H; R = C_6H_5), mp 253–255°, lit. [26] mp 250°. [b]All compds were analyzed for C, H, N.

Scheme 1

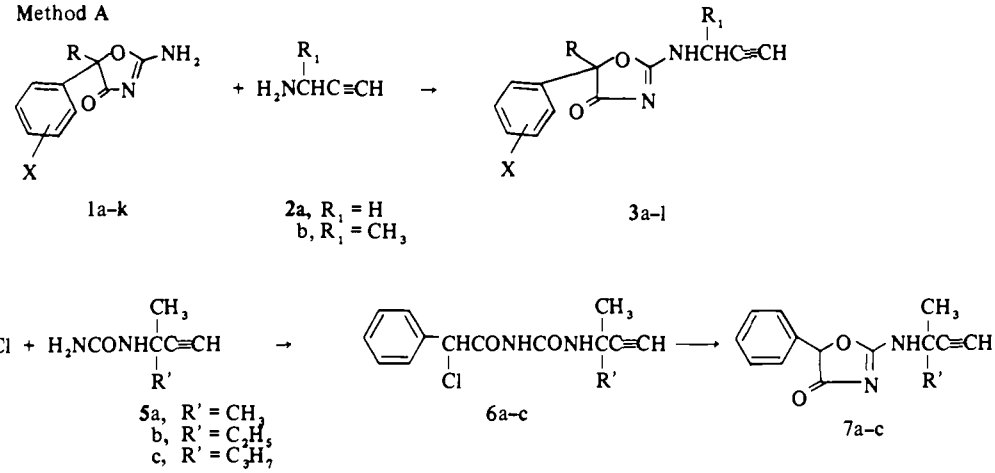
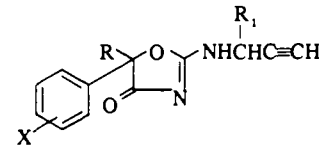


Table II. 5-Phenyl-2-(2-propynylamino)-2-oxazolin-4-one and Derivatives



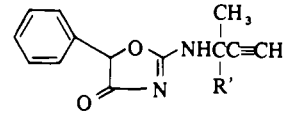
Compd	X	R	R_1	Mp, °C	Yield, %	Crystn solvent	Formula[b]
3a	H	H	H	166–167	50	EtOH	$C_{12}H_{10}N_2O_2$
3b[a]	4-Cl	H	H	180–182	32	EtOH	$C_{12}H_9ClN_2O_2$
3c	2-F	H	H	182–183	33	EtOH	$C_{12}H_9FN_2O_2$
3d	3-CF_3	H	H	190–191	21	EtOH	$C_{13}H_9F_3N_2O_2$
3e	2-CH_3	H	H	134–136	36	EtOH-H_2O	$C_{13}H_{12}N_2O_2$
3f	4-$CH(CH_3)_2$	H	H	117–118	23	EtOH-H_2O	$C_{15}H_{16}N_2O_2$
3g	4-OCH_3	H	H	161–162	29	EtOH	$C_{13}H_{12}N_2O_3$
3h	4-OC_5H_{11}	H	H	139–141	30	EtOH	$C_{17}H_{20}N_2O_3$
3i	3,4,5-$(OCH_3)_3$	H	H	177–178	30	EtOH	$C_{15}H_{16}N_2O_5$
3j	H	CH_3	H	156–157	26	EtOH-H_2O	$C_{13}H_{12}N_2O_2$
3k	H	C_6H_5	H	115–117	57	EtOH-H_2O	$C_{18}H_{14}N_2O_2$
3l	H	H	CH_3	163–164	17	*i*-PrOH-Skelly B	$C_{13}H_{12}N_2O_2$

[a]Prepd in this laboratory by Miss Akiyo Kuroda. [b]All compds were analyzed for C, H, N.

C_6H_6 yielded the acylurea intermediates (**6a–c**) which were cyclized to **7a–c** by heating with 1 equiv of NaOEt in EtOH. 2-[*N*-Methyl-*N*-(1-methyl-2-propynyl)amino]-5-phenyl-2-oxazolin-4-one (**8**) was obtained by heating 2-amino-5-phenyl-2-oxazolin-4-one with excess *N*-methyl-1-methyl-2-propynylamine (see Experimental Section). A higher homolog, 2-(3-butynylamino)-5-phenyl-2-oxazolin-4-one (**9**), was also synthesized by action of 2-amino-5-phenyl-2-oxazolin-4-one with 3-butynylamine in EtOH.

Pharmacology. These compounds were evaluated for antidepressant activity by the mouse dopa response potentiation test[23] (Table IV), and **3a** (propargylpemoline) was found to be the most active member of the series. Further comparative studies with **3a** were carried out to evaluate potency and duration of action (Table V). Propargylpemoline (**3a**) was found to exhibit significant activity at a dose of 2.5 mg/kg at 4, 8, and 24 hr. This unusual potency, as well as duration of action, could be further contrasted to pemoline itself which showed similar activity at doses of 10 mg/kg at 4 hr, 25 mg/kg at 8 hr, and 100 mg/kg at 24 hr. Finally, methylphenidate only showed comparable activity at doses of 50 mg/kg at 4 and 8 hr. Thus, in mice, propargylpemoline is not only more potent than pemoline itself as well as methylphenidate, but also has an unusual long duration of action (24 hr) following a single dose (2.5 mg/kg). Further studies with propargylpemoline in mice indicated that it did not inhibit monoamine oxidase activity in the brain since it did not alter biogenic amine levels in the brain (Table VI).[24]

Table III. 2-[(1,1,-Dialkyl-2-propynyl)amino]-5-phenyl-2-oxazolin-4-ones



Compd	R'	Mp, °C	Yield, %	Crystn solvent	Formula[a]
7a	CH_3	165–166	40	EtOH	$C_{14}H_{14}N_2O_2$
7b	C_2H_5	128–131	20	EtOH-H_2O	$C_{15}H_{16}N_2O_2$
7c	C_3H_7	122–148	16	Cyclohexane-*i*-PrOH	$C_{16}H_{18}N_2O_2$

[a]All compds were analyzed for C, H, N.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir and nmr were determined for most of the compounds. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical value.

2-Amino-5-(*m*-trifluoromethylphenyl)-2-oxazolin-4-one (1d). A soln of 29.8 g (0.12 mole) of ethyl *m*-trifluoromethylmandelate in 60 ml of EtOH was stirred with a filtd guanidine soln prepared from 11.9 g (0.125 mole) of guanidine·HCl in 60 ml of EtOH and 2.9 g

Table IV. Antidepressant Activity in the Mouse Dopa Response Potentiation Test

Compd	Approx LD_{50} oral, mg/kg	Antidepressant act. (oral route, 4 hr), behavioral rating[a,b] 25 mg	100 mg
3a	230	3	3
3b	400	2	2
3c	400	1	2
3d	>1000	1	1
3e	250	1	2
3f	>1000	1	1
3g	>1000	2	3
3h	>1000	1	1
3i	>1000	2	2
3j	400	1	1
3k	400	1	1
3l	300	1	1
7a	850	1	2
7b	750	2	2
7c	>1000	1	1
8	250	1	2
9	400	1	2

[a]Behavioral rating: 1 = slight potentiation; 2 = moderate; 3 = marked. [b]Four mice per dose.

Table V. Comparative Antidepressant Activity of Propargylpemoline, Pemoline, and Methylphenidate in the Mouse Dopa Response Potentiation Test

Oral dose,[b] mg/kg	Behavioral rating[a] 4 hr	8 hr	24 hr
	Propargylpemoline (3a)		
1.25	1	1	1
2.5	2	2	2
5	2	2	2
10	3	2	2
25	3	3	3
50	3	3	3
100	3	3	3
	Pemoline		
5	1		
10	2	1	
25	2	2	1
50	3	3	1
100	3	3	2
	Methylphenidate		
25	1	1	
50	2	2	
100	3	2	

[a]See footnote *a*, Table IV. [b]Four mice per dose.

Table VI. Propargylpemoline and Biogenic Amine Levels in the Brain

	Mouse brain concentration (μg/g ± SE)[a] Dopamine	Norepinephrine	Serotonin
Controls	0.97 ± 0.01	0.52 ± 0.01	0.58 ± 0.01
Propargylpemoline (3a), 50 mg/kg	0.96 ± 0.02	0.50 ± 0.01	0.59 ± 0.01

[a]Mean of 12 mice ± standard error.

(0.125 g-atom) of Na in 60 ml of EtOH. After stirring at room temp for 72 hr, the product was filtd and recrystd.

Compd 1i was similarly prepared; **1f** and **1h** were obtained after refluxing the reaction mixt for 3 hr; 1e was prepared by heating the mixt for 8 hr, and the product was isolated by addition of H_2O and neutralization with AcOH.

5-Phenyl-2-(2-propynylamino)-2-oxazolin-4-one (3a). A mixt of 17.6 g (0.1 mole) of 2-amino-5-phenyl-2-oxazolin-4-one, 11.0 g (0.2 mole) of 2-propynylamine, and 500 ml of EtOH was stirred and refluxed for 70 hr. The soln was concd *in vacuo*, and the product was filtd and recrystd.

Compds 3e, 3f, 3j, and 3k were prepared as above; 3b–d, 3g–i, and 3l were obtained in the same manner except that the mixt was refluxed for 90 hr.

1-(1,1-Dimethyl-2-propynyl)urea (5a). A soln of 62.0 g (0.765 mole) of KCNO in 150 ml of H_2O was added dropwise to a stirred soln of 91.3 g (0.765 mole) of 1,1-dimethyl-2-propynylamine·HCl in 120 ml of H_2O. The mixt was stirred at room temp for 5 hr. The product was filtd and dried: mp 155–156°; yield, 80.2 g (83%). *Anal.* ($C_6H_{10}N_2O$) C, H, N.

Compds 5b[27] and 5c were prepared in the same manner; 5c was isolated as an oil by extn with ether: n^{24}D 1.4851; 89% yield. *Anal.* ($C_8H_{14}N_2O$) C, H, N.

1-(α-Chlorophenylacetyl)-3-(1,1-dimethyl-2-propynyl)urea (6a). A soln of 18.9 g (0.1 mole) of α-chlorophenylacetyl chloride in 50 ml of C_6H_6 was added dropwise to a stirred suspension of 25.2 g (0.2 mole) of 1-(1,1-dimethyl-2-propynyl)urea in 150 ml of C_6H_6. The mixt was stirred at room temp for 1 hr and then heated under reflux for 4 hr. The hot soln was decanted and evapd *in vacuo*. The residue was triturated with H_2O and recrystd from EtOH: mp 105–107°, 10.4 g (37%), *Anal.* ($C_{14}H_{15}ClN_2O_2$) C, H, N; compd 6b, mp 109–113°, 49% yield, *Anal.* ($C_{15}H_{17}ClN_2O_2$) C, H, N; compd 6c, mp 113–140°, 28% yield, *Anal.* ($C_{16}H_{19}ClN_2O_2$) C, H, N.

2-[(1,1-Dimethyl-2-propynyl)amino]-5-phenyl-2-oxazolin-4-one (7a). A suspension of 5.57 g (0.02 mole) of 1-(α-chlorophenylacetyl)-3-(1,1-dimethyl-2-propynyl)urea in 35 ml of EtOH was added gradually to a stirred soln of 0.46 g (0.02 g-atom) of Na in 25 ml of EtOH. The mixt was stirred at room temp for 1 hr and then refluxed for 2 hr. On cooling, the mixt was filtd to remove NaCl. The filtrate was evapd *in vacuo*, and the residue was triturated with H_2O, refrigerated, filtd, and recrystd.

Compds 7b and 7c were prepared in the same manner except that after heating, the mixt was evapd *in vacuo*. The residue was made strongly basic with 15% aqueous NaOH and extd with ether. The aqueous soln was neutralized with AcOH and the oil, which separated, was recrystd.

2-[*N*-Methyl-*N*-(1-methyl-2-propynyl)amino]-5-phenyl-2-oxazolin-4-one (8). A mixt of 17.6 g (0.1 mole) of 2-amino-5-phenyl-2-oxazolin-4-one and 41.5 g (0.5 mole) of *N*-methyl-1-methyl-2-propynylamine was stirred and heated in an oil bath at 140° for 28 hr. The excess amine was removed by distn under reduced pressure, and the residue was recrystd from aqueous EtOH: mp 152–153°; 6.5 g (27%). *Anal.* ($C_{14}H_{14}N_2O_2$) C, H, N.

2-(3-Butynylamino)-5-phenyl-2-oxazolin-4-one (9). A mixt of 31.9 g (0.18 mole) of 2-amino-5-phenyl-2-oxazolin-4-one, 25 g (0.36 mole) of 3-butynylamine, and 650 ml of EtOH was refluxed, with stirring, for 72 hr. The soln was evapd to dryness *in vacuo*, and the residue was recrystd from *i*-PrOH, giving 12.9 g (31%) of the product: mp 117–118°. *Anal.* ($C_{13}H_{12}N_2O_2$) C, H, N.

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Lincomycin. 14. An Improved Synthesis and Resolution of the Antimalarial Agent, 1′-Demethyl-4′-depropyl-4′(*R*)- and -(*S*)-pentylclindamycin Hydrochloride (U-24, 729A)[1]

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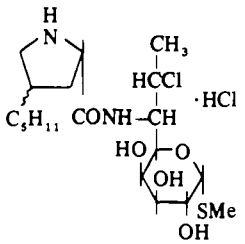
The synthesis of racemic 4-*n*-pentylproline hydrochloride (7) in high yield from α-*n*-pentylacrolein and diethyl acetamidomalonate is described. 4-*n*-Pentylproline is the key intermediate in a practical synthesis of the antimalarial and antibacterial agent, 1′-demethyl-4′-depropyl-4′(*R*)- and -(*S*)-*n*-pentylclindamycin hydrochloride (1) (U-24,279A).

1′-Demethyl-4′-depropyl-4′(*R*)- and -(*S*)-*n*-pentylclindamycin hydrochloride (U-24,729A) (1), a derived antibiotic related to lincomycin and clindamycin, was reported to possess broad-spectrum *in vitro* antibacterial activity and also significant *in vivo* activity.[2] The effectiveness of 1 as an antimalarial agent against *Plasmodium berghei* in the mouse was reported by Lewis[3] who also showed that 1 was not cross resistant with chloroquine or dimethyl diphenyl sulfone. Curative activity against blood inoculated *Plasmodium cynomolgi* in rhesus monkeys was also described.[4]

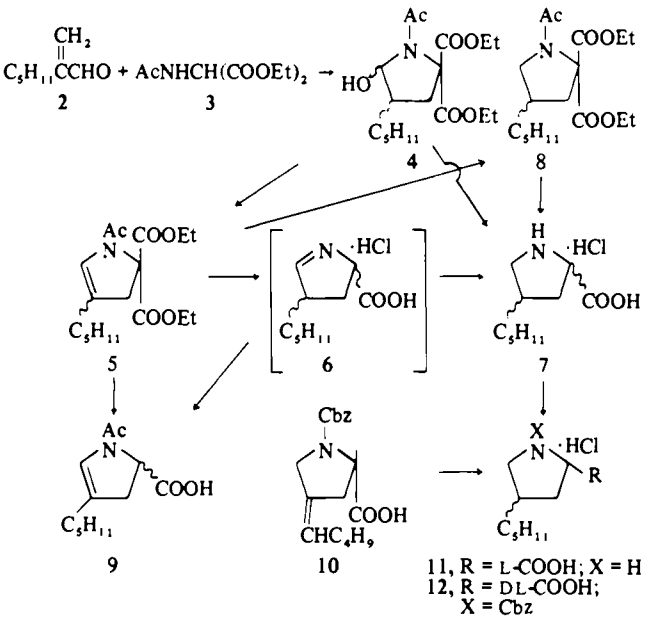


1

We have previously disclosed two closely related sequences for the synthesis of 4′-alkyl-1′-demethyl-4′-depropylclindamycin.[2b] In each case, the amino acid moiety was synthesized by a multistep process having as its key intermediate relatively expensive 1-carbobenzoxy-4-keto-L-proline. We now describe an efficient synthesis of racemic 4-*n*-pentylproline hydrochloride (7) and its facile conversion to 1′-demethyl-4′-depropyl-4′(*R*)- and -(*S*)-*n*-pentylclindamycin hydrochloride (1) in high yield.

The reaction sequence for the synthesis of racemic 4-*n*-pentylproline hydrochloride (7) outlined in Scheme I is similar to the synthesis of racemic 4-*n*-propylproline hydrochloride,[5] but possesses significant process improvements. α-*n*-Pentylacrolein (2), prepared by the method of Green and Hickinbottom,[6] was condensed with diethyl acetamidomalonate (3) to form pyrrolidine 4. While reduction of 4 with zinc-hydrochloric acid[7] gives 7 directly, higher yields of superior quality 7 were obtained as follows. Dehydration of 4 by anhydrous acid yielded 5 which in the presence of refluxing aqueous acid was hydrolyzed and decarboxylated to form acid 6. Catalytic reduction of 6 led to the isolation

Scheme I



of crystalline 4-*n*-pentylproline hydrochloride (7). The overall yield of 4-*n*-pentylproline hydrochloride (7) from diethyl acetamidomalonate, without isolation of intermediates, was consistently 65–70%.

Acylation of non-ultraviolet-absorbing 2-carboxy-4-*n*-pentyl-5-pyrrolidine hydrochloride (6) with acetic anhydride–pyridine[8] gave 45% yield of an acid, possessing ultraviolet absorption at 236 nm, whose nuclear magnetic resonance, infrared, and high-resolution mass spectral data indicate acid 9, previously prepared by saponification and decarboxylation of 5. On this basis the position of the unsaturation in intermediates 5 and 6 was assigned as shown.

Variations in the order of the steps required to convert the initial condensation product 4 to 4-*n*-pentylproline (7) such as 5 → 8 → 7, seemed to offer no advantage over the original pathway.

cis- and *trans*-4-*n*-pentyl-L-proline hydrochloride (11) was prepared by concomitant hydrogenation–hydrogenolysis