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Synthesis and Antihypertensive Activity of 2-Arylamino-1-azacycloalkenes

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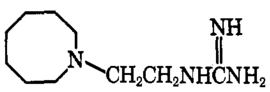
A series of 2-arylamino-1-azacycloalkenes (**3**) was synthesized and evaluated for antihypertensive activity. The compds were generally prepared by treating the cyclic imidoyl chlorides (**6** and **7**) with primary aromatic amines and, in one case, by the Beckmann rearrangement of cyclopentanone oxime with $PhSO_2Cl$ in the presence of 2,6-dichloroaniline. A discussion of the structure-activity relationships in this series is presented.

A number of acyclic and cyclic guanidines have been shown to possess potent antihypertensive activity.[1] Guanethidine (**1**), an example of an acyclic guanidine, has been used extensively for the treatment of hypertension in man. Recently, the cyclic guanidine derivative clonidine[2] (**2**) was reported to provide effective antihypertensive therapy at doses of 0.2 to 4.8 mg/day without incidence of postural hypotension.[3] Replacement of the guanidine moiety in guanethidine with an amidine group has afforded a derivative with potent antihypertensive activity.[4] This paper will discuss the synthesis of certain amidine analogs of clonidine,[5] namely, the 2-arylamino-1-azacycloalkenes (**3**), and will focus on the structure–activity relationships observed in this amidine series.



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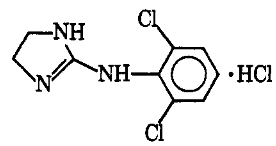

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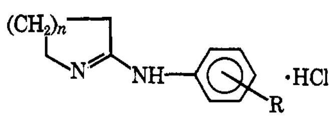

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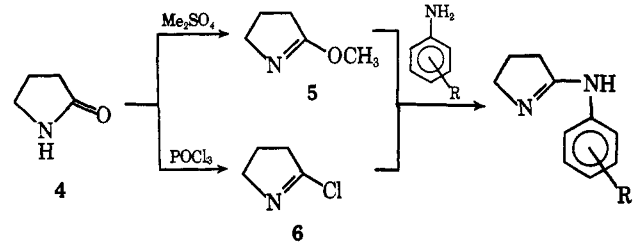
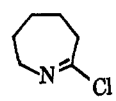
Chemistry.—The 2 reported syntheses of 2-anilino-1-pyrroline (**8**) involve conversion of the lactam, 2-pyrrolidinone (**4**), to either the iminoether[6] (**5**) or the imidoyl chloride[7] **6** and subsequent aminolysis of these reactive intermediates with $PhNH_2$. Attempts at applying Etienne's method[6] by treating 2-methoxy-1-pyrroline (**5**) with a series of ring-substituted anilines gave poor results. While this method failed with the poorly nucleophilic primary aromatic amines, it provided **25** and **26** in good yields when the correspondingly more reactive primary aliphatic amines were used. Compds **8–24**, listed in Tables I and II, were obtained by treating 2-pyrrolidinone with $POCl_3$, followed by treatment of the imidoyl chloride **6**, formed *in situ*, with the corresponding aromatic amine. The tetrahydroazepine derivative **23** was synthesized in an analogous manner *via* the cyclic imidoyl chloride **7**, using ε-caprolactam, $POCl_3$, and 2,6-dichloroaniline.

An alternate approach is demonstrated in the preparation of **22** by applying the Beckmann rearrangement of ketoxime sulfonate esters in the presence of amines.[8] Treatment of cyclopentanone oxime with $PhSO_2Cl$ in base followed by rearrangement of the ketoxime sulfonate in the presence of 2,6-dichloroaniline afforded **22**.





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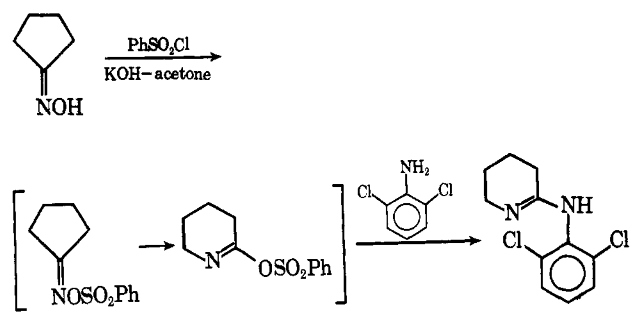

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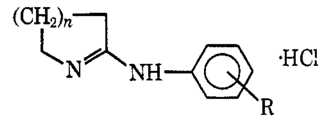
Pharmacology. Methods.—Compds were tested for hypotensive effects in unanesthetized hypertensive rats of the Charles River strain. Weanling male rats were rendered hypertensive by sc implanatation of a pellet contg 20 mg of desoxycorticosterone acetate. A 1% saline soln was administered in the drinking water. After 5 weeks, the carotid artery was cannulated for direct blood pressure measurement by a modification of the method of Popovic.[9] After control pressure measurements, compds were administered intragastrically to groups of 3 rats at 10 mg/kg in saline (5 ml/kg). Direct mean arterial blood pressure was measured at 1, 2, 3, 4, and 24 hr following compd administration. Blood pressure changes were statisti-

(1) O. Schier and A. Marxer, *Fortschr. Arzneimittelforsch.*, **13**, 101 (1969).
(2) Catapres, Catapressan.
(3) A. Khan, G. Camel, and H. M. Perry, Jr., *Curr. Ther. Res.*, **12**, 10 (1970).
(4) E. Schlittler, J. Druey, and A. Marxer, *Fortsch. Arzneimittelforsch.*, **4**, 297 (1962).
(5) While this work was in progress, the following patent was issued: H. Wollweber, R. Hiltman, and K. Stoepel, South African Patent 6802,296 (1968); *Chem. Abstr.*, **70**, 68177 (1969).
(6) A. Etienne and Y. Correia, *Bull. Soc. Chim. Fr.*, 3704 (1969).
(7) H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961).
(8) P. Oxley and W. F. Short, *J. Chem. Soc.*, 1514 (1948).
(9) V. Popovic and P. Popovic, *J. Appl. Physiol.*, **15**, 727 (1960).

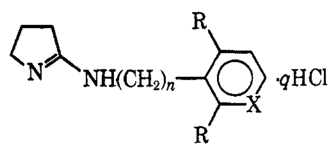
TABLE I
2-ARYLAMINO-1-AZACYCLOALKENE HYDROCHLORIDES



No.	n	R	Mp, °C	Crystn solvent[a]	Formula[b]
8	1	H	217–218.5	A	$C_{10}H_{12}N_2 \cdot HCl$
9	1	2-CH_2	162–164	B	$C_{11}H_{14}N_2 \cdot HCl$
10	1	3-CH_3	171–173	A	$C_{11}H_{14}N_2 \cdot HCl$
11	1	4-CH_3	177–179.5	A	$C_{11}H_{14}N_2 \cdot HCl$
12	1	2,3-$(CH_3)_2$	213–215	A	$C_{12}H_{16}N_2 \cdot HCl$
13	1	2,4-$(CH_3)_2$	171–172	A	$C_{12}H_{16}N_2 \cdot HCl$
14	1	2,5-$(CH_3)_2$	183–186	A	$C_{12}H_{16}N_2 \cdot HCl$
15	1	2,6-$(CH_3)_2$	189–190	A	$C_{12}H_{16}N_2 \cdot HCl$
16	1	3,4-$(CH_3)_2$	222–223	A	$C_{12}H_{16}N_2 \cdot HCl$
17	1	3,5-$(CH_3)_2$	159.5–161	B	$C_{12}H_{16}N_2 \cdot HCl$
18	1	2-CF_3	271–272	C	$C_{11}H_{11}F_3N_2 \cdot HCl$
19	1	3-CF_3	184–188	A	$C_{11}H_{11}F_3N_2 \cdot HCl$
20	1	2,6-$(C_2H_5)_2$	122–124	D	$C_{14}H_{20}N_2 \cdot HCl$
21	1	2,6-Cl_2	258–260	E	$C_{10}H_{10}Cl_2N_2 \cdot HCl$
22	2	2,6-Cl_2	283–284	A	$C_{11}H_{12}Cl_2N_2 \cdot HCl$
23	3	2,6-Cl_2	>280	A	$C_{12}H_{14}Cl_2N_2 \cdot HCl$

[a] A = EtOH–Et_2O, B = EtCOMe, C = MeCN, D = EtCOMe–Et_2O, E = *i*-PrOH–Et_2O. [b] All compds were anal. for C, H, N, Cl, and were within ±0.4% of the theor values.

TABLE II
2-ARYL- AND ARALKYLAMINO-1-PYRROLINES



No.	n	X	R	q	Mp, °C	Crystn solvent[a]	Formula[b]
24	0	N	H	2	216–217	A	$C_9H_{11}N_3 \cdot 2HCl$
25	1	CH	Cl	1	>280	B	$C_{11}H_{12}Cl_2N_2 \cdot HCl$
26	2	CH	Cl	1	238.5–240.5	B	$C_{12}H_{14}Cl_2N_2 \cdot HCl$

[a] A = EtOH, B = EtOH–Et_2O. [b] See footnote *b*, Table I.

TABLE III
ANTIHYPERTENSIVE ACTIVITY OF 2-AMINO-1-AZACYCLOALKENES

No.	Pretreatment average, mm	% change[a] at various time intervals after administration of test compd (10 mg/kg) 1 hr	2 hr	3 hr	4 hr	24 hr
8	180	0	−6	−7	−14	−24
9	151	0	−8	−14	−9	0
10	146	0	−10	−12	−9	−8
11	172	0	0	0	0	−6
12	154	−12	−8	−10	−11	−10
13	176	−11	−14	−19	−16	−12
14	154	0	0	0	0	0
15	186	−10	−30	−43	−35	0
16	181	0	0	0	0	0
17	139	0	0	0	0	0
18	145	0	0	−8	−8	−6
19	142	0	0	0	−4	−10
20	184	0	0	0	0	−23
21	162	−13	−22	−18	−14	−9
22	165	−8	−8	−7	−8	−5
23	140	−13	−10	0	0	−18
24	160	0	0	0	0	−9
25	188	−5	−14	−12	−11	−13
26	153	0	0	0	0	−6

[a] 0% denotes the per cent change from the pretreatment average was not statistically significant.

cally evaluated using the Students' t test and were considered significant at the 95% confidence level ($P < 0.05$).

Structure–Activity Relationships.—While several of the amidines exhibited significant antihypertensive activity, exact potency comparisons cannot be made due to the variations in the pretreatment averages (see Table III). Certain structure–activity relationships, however, are apparent from the data contained in Table III.

1. Placement of substituents at one (**9**, **12**, **13**) or both (**15**, **21**) of the ortho positions of the benzene ring resulted in significant antihypertensive activity peaking between 2 and 3 hr after administration. By comparison, **8** produced a sustained reduction in blood pressure lasting for 24 hr after administration. The size of the substituent also seems to be important, since the 2,6-Et_2 derivative (**20**) did not produce activity until 24 hr had elapsed.

2. Replacement of the anilino moiety with a β-pyridylamino group (**24**) resulted in the loss of activity.

3. Insertion of CH_2 groups between the exocyclic N and the aromatic ring of the anilino group affected activity. **25**, which possesses a single such CH_2 group, is less active than **21**, and the insertion of a second CH_2 group (**26**) resulted in the complete loss of antihypertensive activity.

4. The size of the azacycloalkene ring seems to have some effect on activity. The compd containing a 5-membered pyrroline ring (**21**) provided more potent

activity than the corresponding 6-membered tetrahydropyridine derivative (**22**), however, extension of this argument to the 7-membered tetrahydroazepine (**23**) cannot be made due to the variability in the pretreatment averages.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are cor. Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements were within $\pm 0.4\%$ of the theor values. Nmr and ir spectra were recorded for all the compds and are consistent with assigned structures.

2-(3,4-Dimethylphenyl)amino-1-pyrroline·HCl (16).—A soln of $POCl_3$ (31.0 g, 0.2 mole) in 20 ml of PhMe was added in dropwise amts to a stirred, cooled (10°) soln of 2-pyrrolidinone (**4**) (34.0 g, 0.4 mole) in 20 ml of PhMe. The temp during the addn (20 min) was maintained at 10–15°, then allowed to return to room temp for 3 hr. A soln of 3,4-xylidene (24.2 g, 0.2 mole) in 20 ml of PhMe was added, and the mixt was heated to reflux overnight. It was cooled to room temp, and the PhMe layer was decanted. The residue was dissolved in 150 ml of H_2O and extd with 150 ml of C_6H_6. NaOH (100 ml, 6 *N*) was then added to the aq layer. The resultant alkaline mixt was cooled and 27.65 g (73%) of a light tan solid collected, mp 150.5–152.5°. Recrystn from MeCN yielded light tan crystals, mp 151–153°. *Anal.* ($C_{12}H_{16}N_2$) C, H, N.

The HCl salt was prepd in Et_2O by addn of Et_2O satd with dry HCl. Recrystn from EtOH–Et_2O gave a colorless powder, mp 222–223°. *Anal.* ($C_{12}H_{16}N_2 \cdot HCl$) C, H, N, Cl.

2-(2,6-Dichlorophenyl)amino-3,4,5,6-tetrahydropyridine·HCl (22).—A cold (−10°), stirred soln of cyclopentanone oxime (9.9 g, 0.1 mole), 2.5 *N* KOH (50 ml), and Me_2CO (10 ml) was treated dropwise with $PhSO_2Cl$ (18 g, 0.1 mole). The temp of the resultant mixt was maintained at −10° for 1 hr. The reaction mixt was then extd with 100 ml of C_6H_6, and the C_6H_6 ext was washed with 50 ml of H_2O and dried ($MgSO_4$). 2,6-Dichloroaniline (16.2 g, 0.1 mole) was then added to the dried C_6H_6 ext, and the mixt was heated to reflux overnight. The reaction mixt was cooled to room temp and extd with H_2O (2 × 75 ml). The aq ext was made alk by adding 30 ml of 2.5 *N* NaOH. The alk mixt was cooled in ice water, and 1.6 g (7%) of a brown solid, mp 136–141°, was collected. Recrystn (EtOH–H_2O) provided a light tan solid, mp 143–145°, HCl salt, mp 283–284°. *Anal.* ($C_{11}H_{12}Cl_2N_2 \cdot HCl$) C, H, N, Cl.

2-(2,6-Dichlorobenzyl)amino-1-pyrroline·HCl (25).—A soln of 2,6-dichlorobenzylamine·HCl[10] (4.25 g, 0.02 mole) and 2-methoxy-1-pyrroline[11] (3.95 g, 0.04 mole) in 75 ml of $CHCl_2$ was heated to reflux for 48 hr. The reaction mixt was cooled and evapd to dryness *in vacuo*. Trituration of the residue with Et_2O provided 5.05 g (90%) of a colorless solid, which did not melt <280°. *Anal.* ($C_{11}H_{12}Cl_2N_2 \cdot HCl$) C, H, N, Cl.

2-(2,6-Dichlorophenyl)ethylamine Acetate.—A soln of 2,6-dichlorophenylacetonitrile (22.3 g, 0.12 mole) in AcOH (200 ml) was hydrogenated at room temp (4 atm) using Raney Ni catalyst. After consumption of the theor quantity of H_2, the catalyst was filtered, and the filtrate was evapd to dryness *in vacuo*. Recrystn of the residue from EtOAc furnished 18.9 g (63%) of colorless needles, mp 166.5–167.5°. *Anal.* ($C_{14}H_{13}Cl_2NO_2$) C, H.

2-(2,6-Dichlorophenethyl)amino-1-pyrroline·HCl (26).—A soln of 2-(2,6-dichlorophenyl)ethylamine in $CHCl_3$ was prepd by treating the acetate salt (5.0 g, 0.02 mole) with 100 ml of 2.5 *N* NaOH, and then extg the alk mixt with 100 ml of $CHCl_3$. The $CHCl_3$ layer was then added to a soln of 2-methoxy-1-pyrroline (3.95 g, 0.04 mole) in 50 ml of $CHCl_3$. The $CHCl_3$ mixt was heated to reflux for 48 hr and then evapd to dryness *in vacuo*. Recrystn of the residue from petr ether (40–60°) yielded 3.6 g (94%) of brown needles, mp 123.5–125°; HCl salt, mp 238.5–240.5°. *Anal.* ($C_{12}H_{14}Cl_2N_2 \cdot HCl$) C, H, N, Cl.

(10) J. S. Morley, *J. Chem. Soc.*, 1414 (1961).
(11) S. Petersen and E. Tietze, *Chem. Ber.*, **90**, 909 (1957).

Antihypertensive and Monoamine Oxidase Inhibitory Activity of Some Azacycloalkyl-Substituted Benzaldehyde Hydrazone Derivatives

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The hydrazones derived by condensation of certain azacycloalkyl-substituted benzaldehydes with 3-amino-2-oxazolidinone were evaluated for their antihypertensive and MAO-inhibitory activity. Some of these compds were more potent than pargyline in their antihypertensive response. However, they were less active than pargyline as regards MAO inhibition. The most potent compd of the series was *N*-[2-*N*-methylpiperazino-5-nitrobenzylidene]-3-amino-2-oxazolidinone. There was no direct correlation between the antihypertensive effect and MAO inhibition in this series.

Furazolidone, *N*-[5-nitro-2-furfurylidene]-3-amino-2-oxazolidinone, has been reported to produce slow, gradual reduction of arterial blood pressure in patients with primary hypertension when administered orally.[1] Confirmation of the significant hypotensive effect of furazolidone at high doses in hypertensive patients has been provided by other workers.[2] This substance is also reported to produce irreversible inhibition of monoamine and diamine oxidase in the rat liver and brain.[3] *N*-[1-(5-Nitro-2-furyl)ethylidene]-3-amino-2-oxazolidinone, a compd closely related to furazolidone, is reported to produce a slight hypotensive effect in anesthetized dogs.[4] The present report deals with the evaluation of the antihypertensive and MAO-inhibitory activities of certain hydrazones derived by condensation of certain azacycloalkyl-substituted benzaldehydes with 3-amino-2-oxazolidinone.

Chemistry.—Starting from 2-chloro-5-nitrobenzaldehyde[5] the 3-amino-2-oxazolidinone derivative Ic was prepared by treatment of the β-hydroxyethyl hydrazone derivative Ib with $COCl_2$. By treatment of 2-chloro-5-nitrobenzaldehyde, 3-nitro-4-chlorobenzaldehyde,[6] and 3-chloro-4-nitrobenzophenone[7] with cyclic secondary amines, the corresponding substituted

(1) B. Calesnick, *Amer. J. Med. Sci.*, **236**, 736 (1958).
(2) V. C. Desiderio and J. R. Beem, *Proc. Soc. Exp. Biol. Med.*, **100**, 343 (1959).
(3) D. Palm, U. Magnus, H. Grobecker, and J. Jonsson, *Arch. Exp. Pathol. Pharmakol.*, **256**, 281 (1967).
(4) A. I. Eldin, J. P. Buckley, W. J. Kinnard, and M. D. Aceto, *Arch. Int. Pharmacodyn.*, **149**, 434 (1964).
(5) H. Erdmann, *Justus Liebigs Ann. Chem.*, **272**, 148 (1892).
(6) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 20 (1927).
(7) R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, **27**, 1605 (1962).